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RICHARD MILLS PEARCE, JR., M.D., D.Sc.

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RICHARD MILLS PEARCE, JR., M.D.

# RICHARD MILLS PEARCE, JR., M.D., D.Sc.

In recent years few men have exerted so wide an influence on medical education as did Dr. Richard Mills Pearce, Jr. His untimely death in New York City on February 16, 1930, deprived the medical profession of one whose interest, energy and ability had long been dedicated to progress in medical research and the advancement of medical education. As General Director of the Division of Medical Education of the Rockefeller Foundation, a post which he so ably graced from 1920 until his death, Dr. Pearce's activities as an educator were not limited to this country; they were international. The Far East, South America and many of the countries of Europe, notably Poland, England and France, all profited by his wise counsel and ripe experience. Whenever medical institutions on this continent sought to benefit by the help and support of the Rockefeller Foundation, it was invariably his judgment and advice that proved the determining factors.

Born in Montreal, Dr. Pearce received his early education at the Boston Latin School, and his degree in Medicine from Harvard University in 1897. From the beginning of his career he manifested little desire to practise medicine, and turned his attention to pathology. As Resident Pathologist to the Boston City Hospital and Instructor in Pathology to the Harvard Medical School his industry and ability soon attracted the attention of such eminent pathologists as Councilman, Welsh and Flexner. In 1900 Dr. Pearce came to the University of Pennsylvania as one of Dr. Flexner's assistants and not long thereafter he became Assistant Professor of Pathology in that institution. In 1903 he went to Albany, N. Y., as Professor of Pathology and Bacteriology in the Albany Medical School, and at the same time carried on the duties of Director of the Bender Hygienic Laboratory, as well as those of Director of the Bureau of Pathology and Bacteriology of the New York State Department of Health. Five years later Dr. Pearce was made Professor of Pathology in the University and Bellevue Hospital Medical College in New York City. In 1910 he was called back to the University of Pennsylvania, to become the first Professor of Research Medicine in that institution. For one year after his return to the University

of Pennsylvania he was also Professor of Pathology. From that time on until he became associated with the Rockefeller Foundation, ten years later, his entire time was devoted to the successful conduct and development of the new department of Research Medicine. Shortly after the United States entered the World War he was commissioned a Major in the Medical Corps of the Army. In 1918 Dr. Pearce assumed the arduous duties of Chairman of the Medical Division of the National Research Council; his noteworthy accomplishments in this capacity are a matter of record.

It was during the trying days of the World War that Dr. Pearce undertook the temporary Editorship of the AMERICAN JOURNAL OF THE MEDICAL SCIENCES. When the call to active military service made it impossible for those who were editing this Journal to continue their work, it was Dr. Pearce who, with characteristic unselfishness, voluntarily assumed their duties without thought of recognition or recompense. The readers of the JOURNAL can testify to the able way in which that publication was conducted under his direction. At this time it is but fitting that the publishers, as well as those who were then editors of the JOURNAL, should again express their deep and sincere appreciation of the man who so generously rendered such timely and efficient help to them and to the AMERICAN JOURNAL OF THE MEDICAL SCIENCES.

Known throughout the civilized world as a distinguished scientist, teacher, author and educator, Dr. Pearce occupied a position in medicine that cannot readily be filled. His death is an irreparable loss. Nevertheless, to those who have had the privilege of knowing him, it is both a consolation and a satisfaction to realize that his achievements in the field of medical education will live on, and that the years to come, even more than the present, are destined to prove the farsighted wisdom of his constructive policies.

GEORGE MORRIS PIERSOL.

THE

# AMERICAN JOURNAL

# OF THE MEDICAL SCIENCES

MAY, 1930

## ORIGINAL ARTICLES.

### CHRONIC MENINGOCOCCUS SEPTICEMIA.

(CHRONIC MENINGOCOCCEMIA.)

BY HARRY VESELL, M.D.,

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AND

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GWYN, in 1898, stated that up to that time the meningococcus had not been demonstrated in the general circulation and that it had not been known to play the part of a general infective agent. With these preliminary remarks he proceeded to report the first instance in which the meningococcus was found in the peripheral blood. The patient was on Dr. Osler's service, admitted with the diagnosis of typhoid fever. This first case of meningococcus septicemia was one of the acute variety with clinical signs of meningitis on the second day and death on the sixth.

It remained for Soloman, in 1902, to point out first the chronic variety of meningococcus septicemia, that type which lasts several months and in which meningitis does not play so prominent a part or in which it frequently is absent. It is to this type that the following remarks are essentially directed, and it is our intention to review the subject and report a case. Since Soloman's paper many cases of chronic meningococcus infection with very late or no meningeal localization have been described, especially in the French literature. Comparatively little reference is made to this type of the disease in the standard medical textbooks and in English medical

literature. However, in the following classification of meningococcus meningitis, Sir Humphrey Rolleston does give it a distinct place:

1. Fulminating.
2. Ordinary acute.
3. Abortive:
   (*a*) Septicemic.
   (*b*) Meningitic.
4. Chronic:
   (*a*) Cases not treated, or unaffected by treatment.
   (*b*) Septicemic.
   (*c*) Encysted or loculated meningitis, including posterior basilar meningitis.

In describing 4(*b*) he states that meningococcus septicemia may precede, follow or occur without meningeal infection and may suggest malaria or enteric fever.

The title, "Epidemic Cerebrospinal Meningitis," which tends to direct all concern to the meninges and ordinary form of the disease, is the reason given by one author for the neglect and scant notice given to the extrameningeal forms of meningococcus infection and Herrick advocates abandoning the above name on this account. Indeed, the number of cases of meningococcus infection not developing meningitis is sufficiently large to demand consideration.

Netter had observed the chronic septicemic type in 5 of 368 cases of meningococcus infection and even relatively more common in private cases—3 out of 90 (3.3 per cent). We believe this form of the disease sufficiently different from the acute variety to warrant separate consideration.

**Case Report.** Mrs. S. K., aged forty-three years, born in Russia, was admitted to the Beth Israel Hospital on May 11, 1927, complaining of feverishness and headache of four days duration. She stated that for the past four days she had been feeling feverish in the afternoons while in the mornings and evenings this temperature discomfort had not been present. On two occasions, four and three days before admission, she experienced definite rigors. The headache which also came on suddenly with the fever was rather severe. It was almost constant and referred to the whole head.

The past history and family history otherwise were not relevant to the present illness.

Upon admission to the hospital, the patient did not appear very ill but rather seemed to be quite comfortable lying in bed. The temperature was 101° F., pulse, 90 and respirations, 20.

Examination of the head was negative. There were no abnormal neurologic findings. The throat was not congested. Heart and lungs were also normal to the usual methods of examination. Splenic dullness could be made out to extend to the costal margin and on palpation the edge of the spleen could just be felt under the costal arch.

Over the abdomen, back and extremities, there was a diffuse erythematous eruption consisting of small slightly raised, tender, infiltrated, reddened spots ranging from 2 to 15 mm. in diameter. Outside of slight pain or

achiness on motion of knees and elbows, examination of joints was negative. The rest of the general physical, as well as neurologic, investigation proved unyielding.

The results of the laboratory tests were as follows:

The examination of the blood revealed 3,650,000 erythrocytes per c.mm. and 65 per cent hemoglobin (Sahli). There were 8400 leukocytes per c.mm., of which the polymorphonuclears constituted 80 per cent; lymphocytes (small), 18 per cent; transitionals, 2 per cent. Of the polymorphonuclears 2 per cent were eosinophils and 4 per cent were nonsegmented forms. No parasites or abnormal cells were observed. The blood was Type 2 (Moss). The Wassermann, Felix Weil and Widal tests (including tests for paratyphoid A and B), and blood culture were all negative. The blood chemistry was: Urea nitrogen, 10; nonprotein nitrogen, 22; creatinin, 1; blood sugar, 100 mg. per 100 cc. of whole blood. The van den Bergh reaction proved negative on the direct test and gave a reading of 0.3 units on the indirect. The blood serum registered an icteric index of 2.5 units. The urine revealed no abnormalities on routine examination. Roentgenogram showed the lungs to be clear.

The patient's condition remained practically unchanged for four to five weeks. The fever during this time reached 101° to 104° F. daily and was intermittent. The pulse rate not quite proportional to the fever, ranged from 90 to 100. During this period there were frequent recurrences of the eruption on the body, extremities, palms of the hand and soles of the feet—crops appeared to come out with the rise in temperature and lasted several days, fading and leaving a discoloration.

Prostration finally began to develop and a slight jaundice appeared.

Two transfusions were given with very little effect.

On June 3, twenty-seventh day of illness, a blood culture was reported to have 25 colonies on a plate. These bacteria were Gram-negative diplococci and had cultural characteristics of the meningococcus on differential sugars. This blood culture was the fifth taken and was performed with the same routine technique (unenriched media). Three days later, spinal fluid examination for meningococci was negative.

Except for the temperature the patient appeared to be fairly well clinically up to June 14—thirty-eight days after the onset the patient began to complain of headache in the morning. At 2 P.M. she suddenly became comatose. The neck was distinctly rigid; pupils were dilated, the right greater than the left. There was no Kernig or Babinski sign. Spinal tap showed the fluid to be under increased pressure; 25 cc. of cloudy fluid were removed and 25 cc. of an antimeningococcus serum were injected.

June 15: Again after removal of spinal fluid 20 cc. of serum were injected intrathecally—the patient seemed to respond slightly.

June 16: 17 cc. antimeningococcus serum given intrathecally.

June 17: 30 cc. spinal fluid removed—fluid is clearer. Twenty cubic centimeters of serum given (a specially concentrated antibody solution furnished by New York City Board of Health).

June 18: 50 cc. antimeningococcus serum given intravenously.

June 19: 50 cc. antimeningococcus serum given intravenously.

June 22: Condition very low, pupils dilated, do not react readily, eyes bulging and starey, patient is irresponsive. There is a marked Kernig sign and increase in nuchal rigidity. Forty-five cubic centimeters of cloudy spinal fluid removed, 20 cc. of serum given intrathecally. Fifty cubic centimeters of serum given intravenously.

June 23: 60 cc. antimeningococcus serum given intramuscularly; 40 cc. spinal fluid withdrawn and 20 cc. serum introduced. This the specially concentrated antibody solution. Coma deepened. At 9.45 patient had a convulsion, then ceased to breathe.

*Additional Laboratory Data:*

| | Blood count. | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | R.B.C. | Hb. | W.B.C. | Neutr. | Eosin. | Nonseg. poly. | Small lymph. | Trans. |
| May 12 . . | 3,650,000 | 65 | 8,400 | 74 | 2 | 4 | 18 | 3 |
| May 14 . . | 3,450,000 | .. | 11,400 | 75 | 1 | 7 | 15 | 2 |
| Transfusion | 500 cc. | | | | | | | |
| May 18 . . | 3,700,000 | 70 | 16,100 | 61 | .. | 20 | 18 | |
| May 23 . . | 3,950,000 | 60 | 12,000 | 83 | .. | 2 | 17 | |
| June 4 . . | 3,900,000 | 65 | 10,500 | 81 | .. | 8 | 19 | |
| Transfusion | 500 cc. | | | | | | | |
| | 4,050,000 | .. | 11,000 | 76 | .. | 9 | 13 | 2 |
| | 3,300,000 | 65 | 10,000 | 74 | 1 | 5 | 18 | 2 |

*Blood Cultures.* May 11: Sterile. (One blood culture taken outside of hospital—sterile.)
May 16: Sterile.
May 23: Sterile.
June 3: Twenty-five colonies per plate (twenty-seventh day, Gram-negative diplococci).

| | Cerebrospinal fluid. | | | | |
|---|---|---|---|---|---|
| | Pressure. | Albumin. | Glob. | Cu. red. subst. | Bact. |
| May 24 . . Clear | .. | Trace | 0 | 0.04 | |
| June 6 . . Secondary | .. | 2+ | 2+ | 0.04 | |
| June 15 . . 6000 | 2+ | 2+ | .. | .. | Meningococci. |
| June 16 . . 1040 | 2+ | 2+ | .. | .. | |
| June 17 . . 1300 | 3+ | 3+ | 2+ | .. | |
| June 21 . . 2300 | 3+ | 3+ | .. | None | |
| June 23 . . 6100 | 3+ | 3+ | 3+ | None | |

Spinal Wassermann, negative.

**Discussion.** Chronic meningococcus septicemia is usually characterized by a rather sudden onset. Headache, fever and joint pains is the patient's complaint. The headache is neither severe nor has it a particular localization. It may be frontal or it may be present all over the head and is usually constant. The fever is of the intermittent type, ranging from 99° to 102° or 104°, and continues as such throughout the course of the illness, at times with afebrile periods of four to six days. Netter has carefully described the febrile reaction and has some temperature charts which closely simulate the paludal type of intermittent fever. One of Dock's cases had seven consecutive tertian paroxysms of fever.

Joint pains with or without swelling and redness of the joint, may be a prominent feature of onset and range much in severity. While a 10 per cent complication in the acute disease, it is much more frequent in the chronic condition (43 of 68). An arthritis difficult of differentiation from acute articular rheumatism may present itself. With headache, fever and joint pains as the only complaint

and but slight prostration, the disease continues. During the first week, and often during the subsequent course, at irregular intervals and at irregular times, the patient may have chills—true rigors numbering from two to a half dozen or more in all. By the end of the first week a somewhat characteristic rash appears and this quartet of headache, intermittent fever, joint pains and characteristic rash is sufficiently labeling and identifying to some French authors to permit the presumptive diagnosis of chronic meningococcus septicemia.

Other less common modes of onset are as a focal infection such as a tonsillitis, sinusitis, arthritis, or meningitis. At times a slow insidious onset (Merklen, Wolf, Froelich) may inaugurate the illness.

Cases may be part of an epidemic or they may be sporadic. The disease is more prone to occur in adults and especially in males. Of 27 cases of meningococcus septicemia (acute and chronic) reported by Cholier, Giraud and More, only 4 were in females and three-quarters were between the ages of twenty and thirty years. Late spring and early summer are the seasonal preferences.

**Physical Examination.** The patient early in the disease does not appear acutely ill, but rather quite comfortable and he may not even be confined to bed. The rash is quite prominent. It appears during the first week, though not necessarily so. Four of Netter's 5 cases never had a skin eruption, but most of all the other's cases reported did (Soloman, Vignot, Herrick, Morgan, Neergaard, Dock, and so forth). The rash is of the multiform erythematous type, consisting of crops of firm, tender, slightly raised, red to bluish-red nodules from 0.25 to 2 cm. in diameter. They are found especially on the extremities and trunk and occasionally on the face. They tend to fade after several days and then recur. Frequently new crops come out with each rise of temperature and these may last only twelve hours. They have been noticed to disappear with the onset of meningitis. The skin lesion has been likened to erythema multiform with a marked nodose element (Netter). It does not, however, leave the bluish discoloration on disappearance as does erythema nodosum (Morgan). Other types of skin manifestations found are erythema multiforme, erythema nodosum, purpura, petechiæ, lenticular rose spots (Netter) and herpes. Two types of skin lesion may be present together. The rash is possibly due to cutaneous emboli of meningococci (Rolleston and Renault and Cain) or to toxic effect on the capillary endothelium.

Further examination at this early stage usually shows the absence of any signs of meningitis. There is no nuchal rigidity and the Kernig sign is not obtainable. Eyes and the cranial nerves prove to be normal on examination. The accessory sinuses of the head have not been sufficiently studied in these cases to make general statements concerning them. Herrick reports meningococci in empyema of the accessory sinuses. His case number three of sub-

acute meningococcus sepsis without meningitis started with a tonsillitis and sinusitis. The infected sinus was punctured and drained and though no culture of the pus was made, from further observations the infection was probably of meningococcic etiology. His case number six also was one of sinusitis with rash and no meningitis. Here culture of the sinus pus revealed meningococci.

An acute or subacute tonsillitis and pharyngitis is a not infrequent finding, but there are not sufficient reports on cultures from the tonsils and nasopharynx in these cases to draw conclusions as to their infection by the meningococcus. Are they the portal of entry for the chronic sepsis?

Pulmonary involvement in chronic meningococcemia does occur. Meningococcus pneumonia is said to differ from the ordinary pneumonococcic type of primary lobar and bronchopneumonia in having a more insidious onset and it is claimed not to produce pain in the side. Meningococci have been found in the sputum of some cases. Pulmonary infarcts and pulmonary abscesses have been found due to inflammatory thrombosis of a branch of the pulmonary artery and the meningococcus has been obtained from the clot in the artery. In a case of bronchopneumonia following measles, Chickering has recovered the meningococcus by lung puncture.

Casting some doubt on meningococcus pneumonia, Zinsser states that reports of meningococci in bronchial secretion from bronchopneumonia and lobar pneumonia have usually been based upon insufficient bacteriologic evidence.

Of the cardiac complications, endocarditis, pericarditis and myocarditis have been described. Cecil and Soper, in 1911, were able to find 4 cases of meningococcus vegetative endocarditis in the literature. Krumbhaar added 3 in 1918, from the war epidemic. Roads, in 1927, after a careful survey of the literature was able to locate 11 cases most of which were of the acute variety of the disease, though some lasted five to twelve weeks (Mackarell). In some of these cases vegetations with meningococci were found on the mitral and aortic valve. Meningitis was not present in the majority. These cases are considered essentially endocarditis, that is, valvular heart disease due to the meningococcus. Meningococcus myocarditis is extremely rare. Pericarditis is not a very uncommon complication.

The spleen is frequently enlarged; and in most cases sufficiently so to be easily palpable. In 11 cases of both the acute and chronic form of meningococcus septicemia the spleen was enlarged in 9 (Chalier, Giraud and More). Nine of 68 cases collected by Dock had splenomegaly.

Joint manifestations range from mild fleeting arthralgia with no other local signs, to purulent arthritis with markedly swollen and reddened joints. This disturbance comes on early in the disease and rarely does it persist throughout the entire course of the disease although the signs may come and go. The joints of the lower ex-

tremities are the ones most often involved. Several are affected at one time and the involvement tends to be migratory. The purulent type is apt to be localized to one joint.

**Laboratory Data.** Examination of the blood shows a mild to moderate leukocytosis ranging from 10,000 to 15,000. In the cases to be reported, blood counts were taken throughout the course of illness and they ranged from 8400 to 16,100. The percentage of polymorphonuclears was between 70 and 80. Anemia is not marked, the number of red blood cells rarely being greatly diminished. Hemolysis, as evidenced by the van den Bergh test was not indicated in our case. The icteric index was 2.5 and the indirect van den Bergh normal.

It is interesting to note that blood cultures taken early in the disease and even during the first three weeks most frequently reveal no growth. In some cases this may be due to the failure to use properly enriched culture media, but certainly not so in all. In Dock's 68 collected cases, meningococci were found in the blood in 41—15 only when enriched media was used; in 10, cultures were repeatedly sterile; of these 10, enriched media was utilized in 2. In Morgan's first case, the blood culture was positive only on the forty-ninth day of illness and in the second case on the thirty-ninth day. This was the sixth culture. Neergaard reports the cultures positive on the thirty-first and forty-first day. In the following case growth was first obtained on the twenty-seventh day of illness.

A sterile culture, especially one on ordinary media, does not exclude the presence of a bacteriemia. For cultivation of the meningococcus one should use media enriched with blood serum or ascitic fluid, remembering that the meningococcus is practically an obligatory aërobe and grows best at 37° C. and neutral reaction. Without transplants the culture remains alive but a short time. In serum agar the organism may die out in two to three days. Exposed to sunlight and drying the culture will die in twenty-four hours.

Microscopically the Gram-negative intracellular and extracellular diplococcus of Weichselbaum may closely resemble the gonococcus. In making the differential diagnosis, observance of the marked individual size variation of former is of help. With the Neisser stain metachromatic granules in the center of the cell bodies of the meningococcus may be demonstrated. These two organisms should also be separated by their different actions on the sugars. The meningococcus ferments both dextrose and maltose. The gonococcus ferments dextrose but not maltose.

While these methods are helpful, agglutination tests are desirable and add conclusiveness to the diagnosis. The organisms cultured from the patient should be agglutinated by a polyvalent antimeningococcus serum in various dilutions. Some antimeningococcus sera from horses may agglutinate homologous strains in dilutions of 1 to 3000 and other meningococci in 1 to 500 dilutions. Occasionally

the organisms first isolated may prove inagglutinable, while subcultures are agglutinated. Prolonged incubation has been shown to disturb the specificity of agglutination.

The patient's blood serum can be examined for antibodies by agglutination tests with meningococci. In one case meningococci were agglutinated by patients serum in dilution of 1 to 400.

As for the urine, findings, such as albumin, attributable to the fever, may be present. It is extremely rare to find the meningococcus in this fluid, however Netter did obtain this organism on culture of urine withdrawn from the cadaver on three occasions.

The spinal fluid, in cases where signs of meningitis were not present, was normal to every examination. It is considered inadvisable by some to perform a spinal tap in the absence of definite signs of meningitis or strong suspicions thereof. The danger lies in stirring up invasion of the meninges by the organisms already present in the blood stream, because of the disturbance in osmotic relationship between the two fluids and also possibly through the direct local mechanical trauma caused by the lumbar puncture. This, however, is not in agreement with Dock's findings. The cases where meningitis was present, showed typical spinal-fluid findings of meningococcus meningitis. However, the reducing substance, "sugar" may be present in normal amounts due to the organisms' loss of its ability to destroy this in chronic cases.

**Diagnosis.** Diagnosis, as has already been intimated, is rather difficult to make early in the disease. The intermittent fever rigors and the enlargement of the spleen often create suspicions of malaria. The rash in addition to the fever and splenic enlargement may suggest typhoid. If the joint involvement is at all prominent, acute articular rheumatism may be simulated. Brill's disease and subacute bacterial endocarditis (Endocarditis lenta) must frequently be considered. Gonorrheal sepsis usually occurs within a few months of an acute attack. Bacteriologic differentiation here helps. In typical cases with headache, fever of somewhat intermittent type, joint pains and the tender small erythematous nodular skin lesion, the diagnosis of chronic meningococcus septicemia may be entertained even in the absence of a positive blood culture. However, for definite and convincing diagnosis, a positive blood culture should be obtained. Meningococci grown from other places than the blood such as the cerebrospinal fluid, joint effusions, sinus washings, empyema aspirations, may settle any existing doubts. The presence of meningitis at any time during the disease is highly suggestive. Also the incidence of a number of cases of meningococcus meningitis may hint at the proper diagnosis.

**Course.** The average duration of chronic meningococcus septicema is several months. Vignot's 5 cases for example, lasted 85, 65, 69, 113 and 130 days. During a large part of this time the patient's condition may remain strikingly unchanged. Occasionally

there may be periods of comparative well-being when for some few days the patient is symptomless and even out of bed. On the other hand, the onset of meningitis causes an abrupt change in the clinical picture. Meningitis is nearly always a late manifestation when it does occur. Its appearance was noted on: 15 to 20 and 25th day in Netter's cases; 26 to 37 to 70th day in Pierre Louis Marie's cases; 28 and 40th day in Jottrain's cases; 60th day in Soloman's cases; 56th day in Morgan's case; and the 95th day in case of Moriquard, Bertaye and Charleux.

Does the complication meningitis make the outlook more serious? The seemingly apparent answer is not borne out by the reports. Cholier, Giroud and More analyzing this point state that cases without meningitis had a 50 per cent mortality, four deaths in 8 cases of their series, while those cases with meningitis had but a 33 per cent mortality—3 deaths in 9 cases. They believe that the localization in the meninges is favorable and helps the body to rid itself of the general infection.

**Prognosis.** The prognosis in chronic meningococcus septicemia is not always bad. Indeed, Sergent considers meningococcemia, not of the acute type, the most benign of the septicemias and from his observation resulted in 90 per cent cures. In other series mortality ranged from 10 to 50 per cent. Poor prognostic signs are: abundance of eruption, hyperthermia, profuse diarrhea, tachycardia and especially a positive blood culture with many colonies per cubic centimeters.

**Treatment.** No detailed routine treatment for this form of meningococcus infection has been established. However, it is thought that antimeningococcus serum should be given and by the intravenous route. Netter has obtained cessation of fever in 3 cases after 3, 4 and 6 injections. Vignot reported good results on 40 cc. daily. Stirpe obtained a cure with 180 cc. Contrary results are those of Neergaard who, finding no apparent improvement in the patient after the administration of 477 cc. of serum, discarded its use—the patient recovered. In our case, 307 cc. of antimeningococcus serum (polyvalent) were injected. Of this some was a specially concentrated solution made by the New York City Board of Health Laboratories. This serum was given intravenously and intraspinally and intramuscularly but without success. The series is too small to warrant any conclusions.

A strain or species specific antimeningococcus serum is preferable, if it can be obtained readily. However, if the type of meningococcus cannot be determined, the polyvalent antimeningococcus serum in 20 to 40 cc. doses by the intravenous route, given every twelve hours according to the severity of the patient's condition, is probably the best treatment. To assure oneself that the serum to be used is of value, agglutination tests should be performed between the serum to be used and culture of the meningococcus obtained from the patient.

Transfusions, nonspecific protein shock therapy and intravenous injection of colloidal metals all have been used with but little benefit. Fixation abscess and vaccine treatment have been favorably reported on.

**Summary.** Chronic meningococcus septicemia (chronic meningococcemia) was first described in 1902. Its rarity* is possibly more apparent than real (Marie). Scant notice given to this condition is in part due to the title "Epidemic Cerebrospinal Meningitis," which tends to direct all concern to the meninges and ordinary form of meningococcus meningitis.

Chronic meningococcemia is characterized by a rather sudden onset with headache, intermittent fever, joint symptoms, a typical erythematous skin eruption. There is little prostration and the course is long, lasting two to three months. The outcome is usually more favorable than in other septicemias. Meningitis is absent in a large number of cases. When it does occur it comes on late in the illness and apparently does not unfavorably influence the outcome. Other complications are considered. Early diagnosis is difficult, especially because the blood culture is frequently sterile until late in the disease. The treatment is with specific serum. A case is reported.

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## GONORRHEAL ENDOCARDITIS WITH RECOVERY. A CASE REPORT.

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Relatively few cases of proven gonorrheal endocarditis with recovery are recorded. In view of this fact, it seems worthwhile to report the following case. The case represents one in which the diagnosis of gonorrheal endocarditis seems certain. In addition to the unusual feature of recovery, the case is of interest as to the location of valve damage, and concerning the embolic manifestations which occurred. Furthermore, while recovery may have been purely accidental, the case may be of interest from the angle of therapy.

**Report of Case.** M. L., aged twenty-two years, a clerk by occupation, single male, was first seen on February 17, 1928. At this time, the patient had a slight elevation of temperature and he stated that he had been having fever for about a week. He, however, had not been confined to his bed during this time, and he had had no chills. He had had no evidence of rheumatic involvement. He complained only of fever and prostration. His past history was negative, except for a urethral discharge that had been present since early in November of 1927. This urethral discharge had not been recognized as gonorrhea until February 17, 1928, when positive smears were obtained. One year previous to the present illness the patient

had passed an insurance examination in which no cardiac abnormality was noted.

The social history was negative except for the excessive use of cigarettes. The physical examination, at the time he was first seen, was negative except for a slight fever (99.6°) and a thick, yellowish urethral discharge. There was no prostatic enlargement or tenderness and no tenderness over either kidney. There was no evidence of epididymitis. The red blood cell count was 4,160,000, the hemoglobin 77 per cent (Dare), the white blood cell count 11,800. The differential count gave the following figures: large lymphocytes, 24 per cent; endotheliocytes, 1 per cent; large mononuclear cells, 2 per cent; polymorphonyclear cells, 71 per cent; mast cells, 2 per cent. The urine showed a trace of albumin and many pus cells. It was otherwise negative.

The course of the illness may best be presented by recording the daily notes which were made.

February 24, 1929. The patient has had, since first seen, an irregular elevation of temperature and acceleration of pulse rate. He had today, for the first time, a severe chill and, following the chill, a temperature of 105.6°.

February 29, 1929. Routine physical examination is negative except in the following findings concerning the heart. The heart is beating rapidly and out of proportion to the temperature (temperature, 99.6°; pulse, 104). The apex beat is slightly displaced to the left in the fifth interspace, and on percussion one notes slight left-sided widening of the area of cardiac dullness. On auscultation, there is heard in the pulmonary area, a soft, low-pitched systolic murmur. This murmur is heard over a very limited area and is a very slight one. The pulmonic closing sound is split, accentuated and harsh. All other valve sounds are clear. No petechiæ are noted.

*Comment.* The history of acute gonorrhea followed by a febrile course, with a chill and pulse out of proportion to the temperature, occurring after local symptoms have largely disappeared, and in the presence of a low-grade leukocytosis, and the appearance of a murmur in the pulmonary area suggests gonorrheal endocarditis with probable involvement of the aortic or pulmonary valve. The blood pressure is 105 systolic and 65 diastolic.

March 1, 1928. The patient is essentially the same as yesterday. There is a distinct systolic murmur in the pulmonary area. The murmur is a little louder than when last noted.

March 2, 1928. Auscultation of the heart today reveals a very slight, but definite, early diastolic murmur in the pulmonary area. This is the first time that a diastolic murmur has been heard. The systolic murmur has disappeared.

March 3, 1928. The patient had at 10 A. M. today a severe chill. Before this chill his temperature was 99°, his pulse 89. Following the chill his temperature went up to 104° and his pulse to 130. Four hours later the temperature dropped back to essentially its former level. Of late the patient has had frequent, drenching night sweats.

March 7, 1928. The patient had another chill today (5.30 A.M.), but this chill was not followed by the sharp temperature rise previously recorded. The temperature for the past four days has ranged around 101.5° to 102° in the afternoons, dropping in the forenoons to 99° to 100°. The pulse in general has been out of proportion to the temperature. Ausculation of the heart reveals the diastolic murmur previously recorded, best heard in the pulmonary area. It is a louder murmur and now occupies the whole of diastole. The area over which it may be heard is somewhat limited. It is transmitted a short distance down the left border of the sternum.

A positive blood culture, showing a pure growth of gonococci, is reported today. The culture was obtained on a bone-meat infusion agar and the

colonies appeared after four days' incubation. A number of blood cultures have been taken but all had until today been sterile. The blood from which this positive culture was obtained was secured immediately after a severe chill. This had not been true of the samples of blood previously obtained for culture. A vaccine is to be prepared from the culture obtained today.

March 8, 1928. A blood transfusion of 250 cc. of citrated blood is given.

March 9, 1928. A blood transfusion of 250 cc. of citrated blood is given.

March 11, 1928. The patient has been severely ill since the last note. He has had three chills with temperature rise to between 103° and 104°. A transfusion was given him immediately after his chill on March 8, 1928, and appeared to produce no reaction. The transfusion on the ninth was given about four hours after a chill. The pulse and temperature are, in general, proportionate now.

March 14, 1928. A blood transfusion of 250 cc. of citrated blood is given.

March 15, 1928. A blood transfusion of 250 cc. of citrated blood is given.

March 16, 1928. Since the last note the patient has been better. His temperature has not been above 100°. His pulse has been relatively quiet.

March 20, 1928. Examination of the heart shows the right border of cardiac dullness moderately displaced to the right. The diastolic murmur, best heard in the pulmonary area and transmitted down the left border of the sternum, is heard. The blood pressure is 110 systolic and 65 diastolic. No petechiæ are present. It is believed that the valvular involvement is of the pulmonary valve.

March 22, 1928. The patient has been decidedly sicker. Beginning March 16, 1928, his temperature began to show wide excursions, varying 97° to 104°. On March 20 he had a severe chill with temperature rise to 104.3° and a pulse rise to 120. On March 21 his temperature went to 104.4° with his pulse to 135. He continues to have drenching sweats.

March 23, 1928. The patient is given today 150 cc. of serum from a donor who 3 months ago recovered from gonorrheal arthritis.

March 26, 1928. The patient is given today 250 cc. of citrated blood. He has had a low-grade polymorphonuclear leukocytosis from the onset of his illness. Repeated examinations have shown the white cells between 10,000 and 15,000. The patient has at no time shown much reduction in his red-cell count or in the percentage of his hemoglobin. Repeated examinations of the urine have failed to show blood. The urine does show a trace of albumin and occasional casts. Examination of the heart today shows a very striking, harsh, diastolic murmur, best heard in the pulmonary area and transmitted down the left border of the sternum. No murmurs are heard in other valve areas. The blood pressure is 110 systolic and 68 diastolic. There are no peripheral evidences of aortic regurgitation.

March 27, 1928. A blood transfusion of 250 cc. of citrated blood is given.

March 30, 1928. Yesterday at 1.30 P.M., the patient, while feeling quite comfortable, suddenly developed a severe, knifelike pain in the left lower axillary region, making breathing very shallowly and he grunts with each respiration. There is impairment to percussion in the left lower thorax, laterally and posteriorally. Over this area breath sounds are diminished and voice transmission is diminished. The abdomen is markedly bloated with gas. The patient coughs with difficulty and brings up blood-stained material. Immediately following the appearance of the above pain he was profoundly shocked.

April 2, 1928. The patient received today 0.2 cc. of autogenous gonococcus vaccine of a strength of 400,000,000 per cc.

April 4, 1928. A blood transfusion of 250 cc. of citrated blood is given. The small dose of vaccine created no reaction.

April 5, 1928. A blood transfusion of 250 cc. of citrated blood is given. The patient has been running a much lower level of temperature, this since

March 25, 1928. Examination of the heart shows the murmur heretofore described. At present the percussion outline of the heart seems essentially normal. There is possibly slight right-sided widening. The painful condition of the lung has gradually cleared and at present the patient is quite comfortable. There is slight impairment to percussion over the left base with diminution of breath sounds over the area of impairment.

April 10, 1928. A blood transfusion of 250 cc. of citrated blood is given, 0.4 cc. of the above-mentioned vaccine is also given.

April 11, 1928. The injection of the vaccine yesterday was followed by a drop of temperature from 98.6° to 97.5° and followed by a rise of temperature to 101°. The patient experienced a rather severe reaction to the vaccine. The patient's temperature today reached 103.2°, the highest point for the past four days.

April 12, 1928. A blood transfusion of 250 cc. of citrated blood is given.

April 14, 1928. One-half cubic centimeter of the autogenous vaccine today was followed by a severe reaction. To date no appreciable change in the general course of the case has appeared. In view of this, and in view of the patient's dread of the reaction produced by the vaccine, it is thought wise to discontinue its use. The patient developed suddenly today pain in the left upper chest, made worse by deep breathing. This involved the scapular area and pain extended into the neck. The patient was not disturbed for an examination of his chest. He is coughing blood-stained mucus. He appears to have had another pulmonary embolism.

April 16, 1928. The patient's general condition remains the same. His temperature ranges from 99° to 102°. The condition of his heart is essentially the same.

April 18, 1928. The painful condition of the chest gradually disappeared following the occurrence of April 14, 1928. Again today, however, he complains of severe pain in the left upon thorax, and he is again coughing blood. This is taken to be the third pulmonary embolism which has occurred.

April 19, 1928. One very satisfactory feature in connection with the care of this patient is the fact that he has eaten well during practically all of his illness. He has not lost very decidedly in weight. Another feature which bears mentioning is the fact that he has smoked very heavily of cigarettes during the whole course, consuming from 20 to 30 cigarettes a day. He is clinically better, at present.

April 20, 1928. The pain above mentioned has continued to date. It is of a pleural type and has required morphin for relief.

April 23, 1928. A blood transfusion of 250 cc. of citrated blood is given.

April 24, 1928. A blood transfusion of 250 cc. of citrated blood is given.

April 28, 1928. Since the last note the patient has been strikingly better. His temperature has been essentially normal. His pulse in general has been quiet. He is eating well, sleeping well and digesting well.

The diastolic murmur, which seems to originate in the pulmonary valve, is as previously recorded. At no time during the course of the case has there been the blood pressure of an aortic regurgitation. At no time has there been evidence of congestive failure.

April 29, 1928. The patient again has had a pulmonary embolism, characterized by severe pleural pain involving the left base posterially. Following the pain he had a violent chill. His temperature, which had been essentially normal so long, went to 103°, and his pulse to 140. The patient became cyanotic, and he again coughed blood. His condition was so bad that he was not disturbed for examination of his chest, the clinical picture being so strikingly that of an embolism.

May 2, 1928. The patient has had, since the last note, a "steeple" chart. His temperature reached 103° today, his pulse 120.

May 7, 1928. A blood transfusion of 250 cc. of citrated blood is given.

May 8, 1928. A blood transfusion of 250 cc. of citrated blood is given.

May 10, 1928. Following the last embolic manifestation, the patient gradually improved and he now has a normal temperature. His pulse varies between 80 and 100. He is clinically in good condition, at present. The heart murmur remains essentially unchanged. There is very little, if any, right-sided widening and no left-sided widening is apparent on percussion. The blood pressure is 115 systolic and 70 diastolic.

May 30, 1928. The patient is discharged. He has consistently maintained a normal temperature since the last note. His pulse has varied somewhat, but has ranged around 80 beats per minute. He has continued to gain in weight and strength. He has been gradually allowed to sit up during the past week. Final examination of the heart is as last recorded. Examination of the lungs reveals some impairment to percussion over the left base and lower axillary region, with diminution in intensity of breath sounds and of transmitted voice.

August 3, 1928. The patient reports that he is well. He has not attempted strenuous work, but experiences no cardiac difficulty on ordinary exertion.

July 12, 1929. The patient reports by letter that he is well.

**Epicrisis.** In all, fourteen blood transfusions were employed. All transfusions were of 250 cc. of citrated blood. In giving the transfusions the donor was bled 500 cc. and one-half this amount was given, the other half being kept in the icebox and given the following day. No reactions to the transfusions occurred. One injection of 150 cc. of convalescent serum was given.

A limited use of autogenous vaccine appeared to be of harmful effect.

A liberal food intake was maintained throughout the illness. Drug therapy, as indicated for pain and sleep and for bowel elimination, was employed.

A moderate leukocytosis was present throughout the illness. The highest of 20 counts was 15,900, the lowest 9100. In all counts there was a moderate increase in the percentage of polymorphonuclear cells. A marked anemia did not occur. With the numerous transfusions the figures for the red-cell counts and hemoglobin determinations were near normal, throughout the entire course of the case.

Frequent examinations of the urine were made, and commonly a trace of albumin and a few casts were present. Pus, which had been present when the patient was first seen, soon disappeared. The urine at no time showed red blood cells.

The location of the basal murmur, the occurrence of numerous pulmonary emboli, and the absence at all times of the blood-pressure change of aortic insufficiency make the location of the valve damage certainly the pulmonary valve. The patient now represents a true case of acquired pulmonary valvular disease.

A chart showing the high and low temperatures of each day follows.

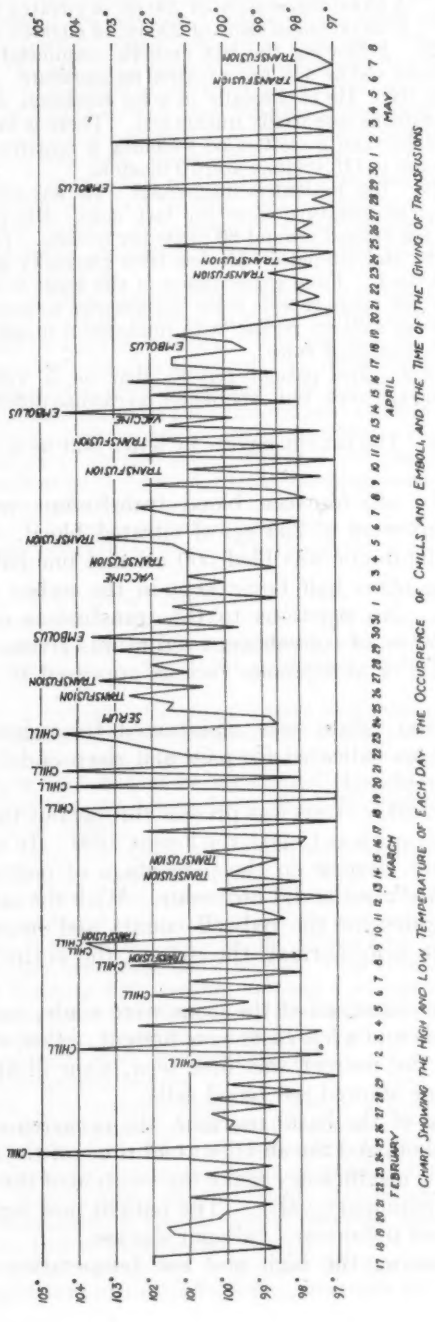


CHART SHOWING THE HIGH AND LOW TEMPERATURE OF EACH DAY THE OCCURRENCE OF CHILLS AND EMBOLI, AND THE TIME OF THE GIVING OF TRANSFUSIONS

**Summary.** 1. A case of gonorrheal endocarditis with recovery is reported.

2. The findings making certain the diagnosis are recorded.

3. The localization of the disease process in the pulmonary valve is shown and the reasons for this localization are given.

4. Treatment of the case is reviewed and emphasis placed on the apparent value of frequent small blood transfusions in this treatment.

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## AURICULAR FLUTTER FOLLOWING DIRECT INJURY TO THE CHEST.

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The effects of direct injury to the chest have, in recent years, been recorded in a number of contributions to the literature. Various types of heart conditions have been described resulting from external violence. The exact pathogenesis of these conditions remains, however, speculative in certain types of cases.

The literature is very scant concerning instances of auricular disturbances that follow direct violence to the chest. What the pathologic changes are that produce this condition one cannot declare with certainty. However, the possibility of subepicardial ecchymosis in the auricular muscle must be considered. The cardiac damage in these cases is not disputable.

Levinson[1] and Kahn[2] have each reported a case of auricular fibrillation that resulted from a blow to the anterior chest wall. Rosenson[3] has described a case of transient heart block produced by a blow. More serious lesions have been described extensively in the literature. Recently, the author has reviewed the subject at some length.

In the present communication, I desire to present a case of unusual interest, as it is the first on record of auricular flutter produced by injury to the chest wall.

**Case Report.** John M., a robust porter, aged fifty-nine years, gave a negative family history. His wife and three children were well; there had been no miscarriages and no history of familial diseases. He had suffered from occasional tonsillitis years ago, and at that time had some stiffness of the joints. Ten or fifteen years before the present illness, he was injured in the left chest by a falling barrel, fracturing some ribs.

The history of the accident is as follows:

On March 11, 1929 at 12.30 P.M., while holding down and leaning over the handle of a crowbar which was forced under a heavy soda fountain,

the handle recoiled, striking the patient twice sharply against the lower left breast region. He screamed out loud with pain, was momentarily dazed and stepped away releasing his hold. He did not fall down, did not faint or become unconscious; did not vomit, and did not cough or expectorate blood.

The sharp pain continued and was localized outside of, and below, the left breast region, but it did not prevent the patient from continuing his regular work that day. In the evening, he applied chloroform liniment, but could not sleep for the pain. He did light work on the day after the accident, and on the following day he was sent by his employer to a physician, who applied adhesive strips to immobilize the left chest. The patient continued work for two days more and then, on returning home, he suddenly fell and almost fainted. That night, he could not sleep because of precordial pain. He has not been able to work since then, but has visited his physician almost daily for "baking" treatment of the left chest.

On March 20, Roentgen ray of the chest revealed old fractures of the eighth and ninth left ribs.

At the time of my examination about three weeks after the injury, the patient complained of weakness, precordial pain, palpitation, and shortness of breath. This was worse on exertion, but also occasionally occurred while at rest. At night, he found difficulty in breathing and had "to sit up for pain." There was occasional dizziness, but no headache; moderate cough and expectoration, but no hemoptysis. There was moderate edema of the legs. Vision and hearing had become somewhat defective.

The physical findings three weeks after the accident were as follows: The eyes, mouth, nose and glands revealed nothing of significance. There was a bilateral chronic catarrhal otitis media with considerable deafness. The skin showed a desquamation in the left axilla with erythema due to physiotherapy. There was a scar of an old carbuncle across the back of the neck.

The right border of the heart percussed 3 cm. from the median line; and the left border 11 cm. from the median line, at the nipple line. The apex beat was felt poorly, diffuse in the fifth space within the nipple line. The heart action was irregular in phases, with occasional extrasystoles. The first sound at the apex was clear and of fair muscular quality. No murmurs were audible. The second aortic sound was slightly accentuated. There was moderate temporal tortuosity and a Sahli capillary zone around the lower chest. The blood pressure was 160 systolic and 100 diastolic, with an alternating pressure of 130 systolic and 100 diastolic, every other beat.

The chest was somewhat asymmetrical with lateral flattening in the left axilla. Expansion was fair and equal. There was some diffuse tenderness over the left lower axilla, more marked over the seventh and eighth ribs in the midaxillary line. There were no palpable fractures, crepitus or deformity. There was no swelling, ecchymosis, or other external evidence of injury. There was moderate supraclavicular retraction.

The lungs gave a hyperresonant note on both sides, anteriorly. Breath sounds were vesicular, and there were atelectatic râles present, which were more marked at the right base posteriorly.

Liver dullness extended from the sixth rib to below the free border, the edge was not distinctly palpable. The abdomen revealed no masses or tenderness. There was a large, right, oblique inguinal hernia protruding into the scrotum. The left inguinal ring admitted the finger tip, but there was no hernia.

Orthopedic examination showed slight scoliosis with convexity to the right. The patient had difficulty in lying down and sitting up because of pain in the left axilla. There was some pain on full extension of the knees. He walked with a gait favoring his left side. The upper extremities showed

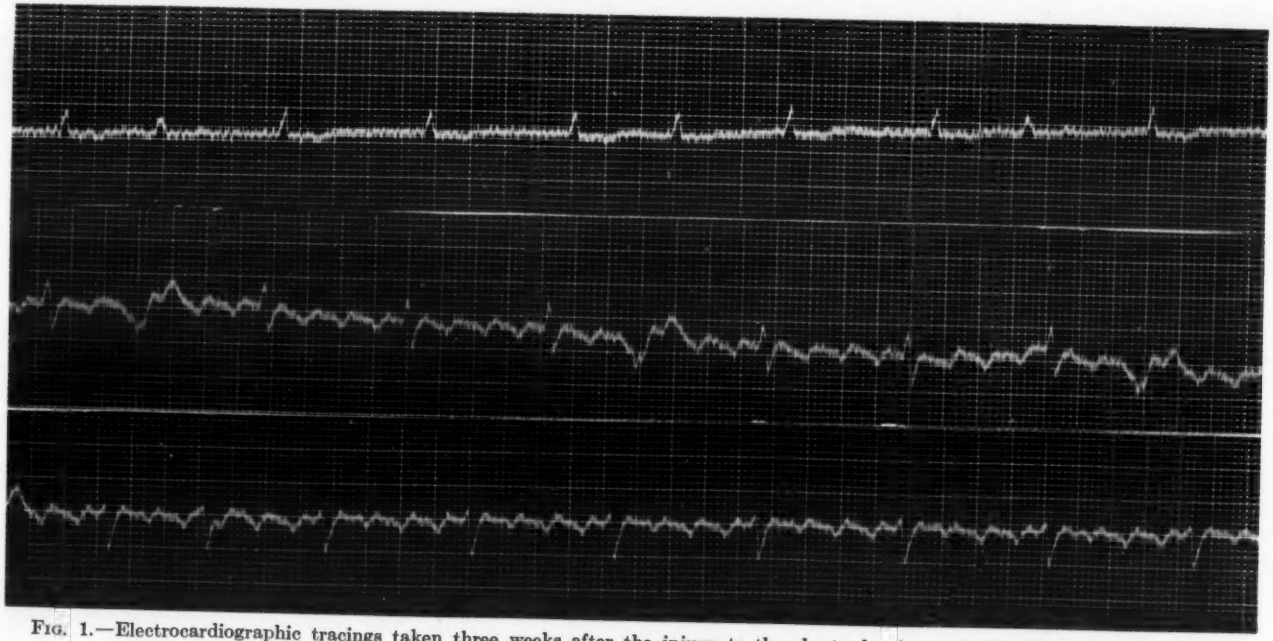

FIG. 1.—Electrocardiographic tracings taken three weeks after the injury to the chest, showing auricular flutter and occasional ventricular premature beats.

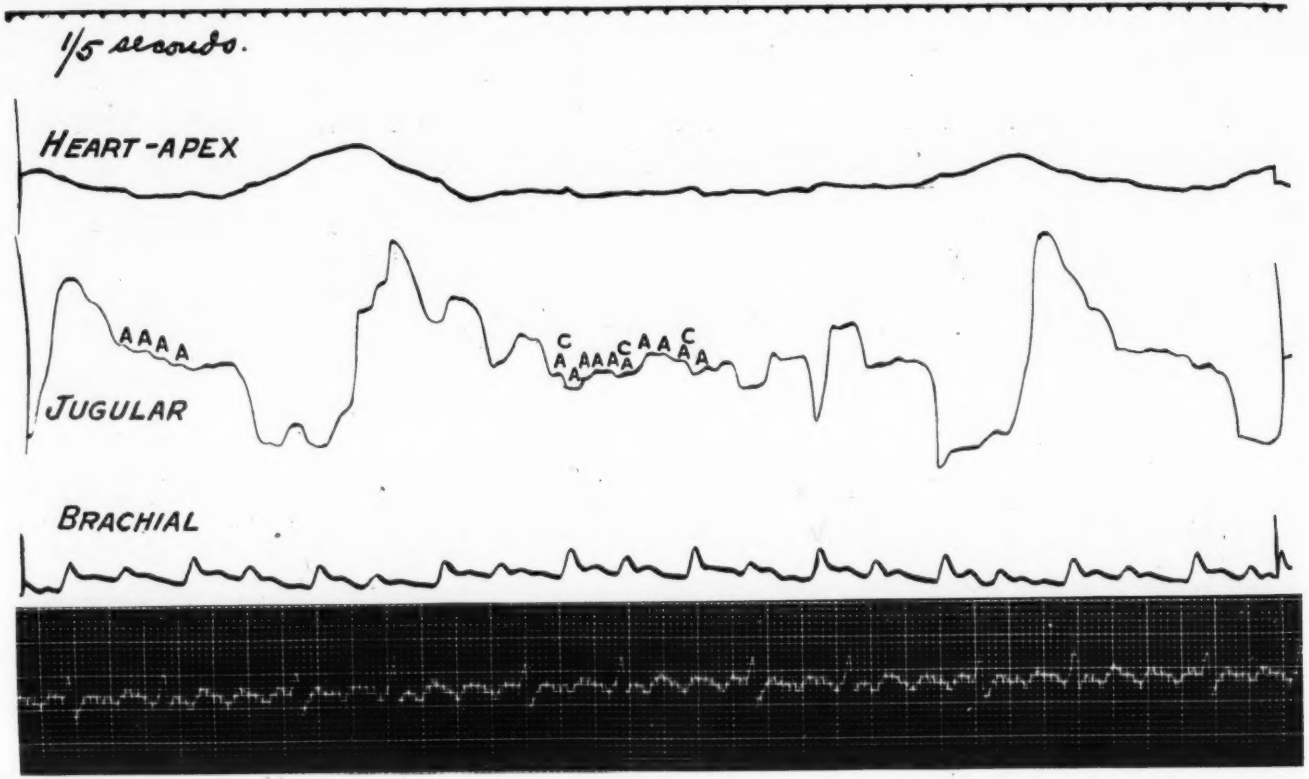


FIG. 2.—Polygraphic and electrocardiographic tracings (Lead II) taken three weeks after the injury to the chest, showing auricular flutter with a rate of 3 to 1 and 4 to 1 in alternating cycles. The jugular curve presents the auricular waves and the brachial tracing shows the alternating amplitude of the waves.

old swelling with Heberden nodosities about the finger joints. There was marked swelling of the lower extremities up to the level of the knees. The tendon reflexes were normal.

The urine showed some albumin, but no casts microscopically. The blood Wassermann test was negative.

Teleroentgenographic examination of the heart and aorta revealed the following: The patient was of hypersthenic habitus. The heart was obliquely oval in shape, and there was increased obliquity of the cardiac axis. It was enlarged in its transverse and longitudinal diameters, and the right auricular and left ventricular curves were accentuated. The aortic arch was sclerosed. The measurements were as follows: Median right, 9 cm.; median left, 9.5 cm.; aorta, 7 cm.; longitudinal, 18 cm.; pulmonic fields, 27 cm.

The polygraphic tracings showed the existence of bigeminy over long periods in which every alternate cycle was extrasystolic followed by a compensatory pause. At other times these extrasystoles were infrequent and a regular pulse was maintained at a somewhat slow rate. The jugular curve showed very characteristically the waves of auricular flutter. The apex tracing was small and trapezoidal.

The electrocardiogram showed left ventricular preponderance. There was an inconstant ventricular rate of about 75 to 80 per minute. The auricular rate was 300 per minute with distinct waves of auricular flutter shown conspicuously in Leads II and III. There was a relative heart block of 4 to 1. At times, the ventricular rate increased over a short period, with a relative 2 to 1 block. There were occasional aberrant waves of conduction through the ventricle with slight distortion of the ventricular cycle. Occasional premature beats occurred, arising from the apex of the right ventricle. During some periods in the electrocardiogram, there was present a 4 to 1 and 2 to 1 alternate relative auriculoventricular block, producing an alternans type of pulse due to the difference in ventricular filling at every other cycle.

The voltage was low in all three leads. There was no widening of the *Q–R–S* wave, and no evidence of myoneural conduction defect.

A month later, the liver was found to be enlarged to four fingers below the costal margin. The edema of the extremities persisted.

The Roentgen ray shadow at this time, showed a slightly increased transverse diameter of the heart, but the occsaional ventricular premature beats and the auricular flutter persisted in the electrocardiogram.

Treatment by digitalis and quinidin, and a strict Karrel diet was ineffectual in producing improvement of the patient's condition which grew progressively worse. Swelling of the scrotum developed and the urine showed an increased amount of albumin with a rare hyaline and numerous granular casts, and occasional red blood cells.

The condition persisted unimproved for another month.

The patient died four months after the accident. Unfortunately a postmortem examination was not made.

**Discussion.** In this case, the cardiac symptoms, including the sharp pain in the precordial region, followed immediately upon the recorded accident. In point of time the onset is therefore closely and directly associated with the injury. In the absence in the history and physical examination of any of the other causes which might induce auricular flutter, such as marked arteriosclerosis, syphilis, hypertension, rheumatism, Grave's disease or any other toxic or infectious conditions, we are led to the assumption that there

FIG. 2.—Polygraphic and electrocardiographic tracings (Lead II) taken three weeks after the injury to the chest, showing with a rate of 3 to 1 and 4 to 1 in alternating cycles. The jugular curve presents the auricular waves and the brachial tracing shows the alternating amplitude of the waves.

was a direct relationship between the alleged accident and the patient's condition.

His previous ability to do hard work certainly gainsays any existence of this condition prior to the alleged direct trauma to the chest. The location of the extrasystolic cycle is particularly suggestive of a relationship, as the right ventricle is most exposed to the effects of direct violence to the anterior chest wall. The pathologic changes that may have taken place from the injury are necessarily speculative. The possibility of subepicardial ecchymosis in the auricular muscle is to be considered. The process takes a long time to heal and therefore the auricular flutter may last an indefinite period of time.

There is an interesting feature suggested by the electrocardiogram that deserves a word of note. In Fig. 2, it is to be noted that the alternate ventricular cycles occur after every four and every two auricular contractions. This produces an arrhythmia which is hardly appreciable as one listens to the auscultatory effects in taking the blood-pressure measurements. The impression then is a distinct pulsus alternans with a difference of 30 mm. in the systolic pressure between alternate cycles. This difference is equivalent to half the pulse pressure. One may judge from this that the auricular function in this case in producing ventricular filling is a most important one. Apparently every contraction of the auricle during flutter contributes its definite measure of blood to the ventricular volume.

Another feature in the electrocardiogram is of great and suggestive interest. It is to be noted that preceding every ventricular cycle that follows two auricular contractions, there is a normal $P$–$R$ interval of 0.2 seconds. When four auricular waves occur, conduction becomes reduced to 0.14 seconds. It is thus seen that there is an improvement of conductivity following the longer periods of block.

We shall have to leave unanswered the question of why in some cases auricular fibrillation occurs as a result of direct injury to the chest; and in this case, auricular flutter. It is possible that the incidence of this condition depends upon the location of the lesion in the auricular musculature, its proximity to the region of the sinus node, and its distribution otherwise throughout the auricular wall.

Whenever a colliding force has been directed against the precordial region of a patient, the possibility of myocardial damage must be kept in mind. If fracture of the ribs or injury to the pleura occurred such suspicion becomes emphasized. The presence of irregular action which supervenes upon violence to the heart is a significant sign. Although the pain has no particular characteristics, it is usually localized over the injured area and sometimes radiates to the left axilla or below the left breast.

It must emphatically be recognized that milder injuries of the

myocardium, consistent with life over a varying length of time, may take place. The symptoms and signs, as well as the disability in such cases, usually persists.

**Summary.** 1. A case is reported in which, following direct violence to the chest, auricular flutter was discovered with signs of heart failure.

2. The pathogenesis of this condition is only to be surmised. The possibility of subepicardial ecchymosis in the auricular muscle is to be considered.

3. Milder injuries of the myocardium may result from direct violence to the chest with consequent disability, although consistent with continued life.

4. The blood pressure findings suggest that a definite amount of ventricular filling is produced by each auricular contraction.

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## THROMBOSIS OF THE HEPATIC ARTERY.

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Thrombosis of the hepatic artery is a pathologic curiosity and has been reported only once before by Lancereaux.[1] Rolleston[2] suggests that this case might have been due to an embolism from thrombi in the vessels of the lower extremities. Embolism of this vessel is also rare but cases have been reported by Chiari[3] and others. Chiari found complete necrosis of the liver, the main trunk of the vessel being involved. Lancereaux[4] and Ogle[5] have reported cases of embolism at the bifurcation. In Ogle's case there were anemic infarcts in the liver but no general necrosis. Septic embolism of the smaller branches of the hepatic artery occurs in hemic infections and gives rise to pyemic abscesses. Embolism occurs in generalized tuberculosis and sarcomatosis (Rolleston[2]). Closure of the smaller vessels is usually not followed by necrosis (Kaufmann[6]).

Friedenwald and Tannenbaum[7] recorded 65 cases of aneurysm of the hepatic artery. In 5 of these cases, the aneurysmal sacs contained thrombi (Ledieu, Riedel, Reichman, Tuffier and Hogler). Three others showed thrombosis of hepatic artery as well as the sacs (Liverato, Teacher and Jack, Merkel). Three showed necrotic areas in the liver (Brion, Bode, Dean and Falconer). In a case of

a small tuberculous aneurysm of a branch of the hepatic artery associated with thrombosis of the portal vein, Thompson[8] found definite infarcts in the liver. Stokes and Inglis[9] reported an aneurysm of the hepatic artery with acute pneumococcic endocarditis raising the question of the infectious nature of this aneurysm.

In this paper, the metabolic changes are not discussed, as they are not brought out in the two cases here reported. These are presented; one from the Laboratory Division of Montefiore Hospital under the supervision of Dr. David Marine, and the second from the Krankenhaus im Friedrichshain, Berlin, through the courtesy of Prof. Ludwig Pick.

**Case Reports.** CASE I.—M. L., male, aged forty-three years, born in Russia, resident of U. S. A. seventeen years, an operator, was admitted to hospital, June 11, 1927. He died June 20, 1927. C. C. Dyspnea. Pain in stumps of both legs. Loss of 40 pounds in one year.

*Present Illness.* Patient had cramplike pains in both legs in 1915, worse on walking, relieved by resting or sitting. In 1916, amputation of the right leg above the knee was performed on account of the development of gangrene of the first and fifth toes. In November, 1921, amputation of the left leg below the knee was performed at the Lebanon Hospital for gangrene of the first toe. The popliteal artery was almost completely obliterated by a fibrotic canalized thrombus with an inflammatory reaction in the coats of the vessel. The diagnosis was thromboangiitis obliterans. Four further operations to upper third of left thigh were performed on account of failure of the stump to heal; last in December, 1926. Pain recurred in both stumps.

In May, 1926, he developed sudden onset of shortness of breath, fear of impending death, choking sensations and pressing pain over the precordium radiating to sternum and up to neck. He was rushed to a hospital where he remained three weeks. He was given digitalis and felt relieved. He spent varying short periods in four institutions for recurrent heart attacks which became more frequent, sometimes two or three in twenty-four hours. On two occasions he expectorated bright-red blood. He had spots before his eyes and diplopia. For two months he had edema of the stumps, constipation, piles, indigestion, nocturia two to three times, urinating three to five times daily. In May, 1927, he had bloody urine for four days. Previous and family history were irrelevant.

PHYSICAL EXAMINATION. Sallow complexion with marked pulsations of the vessels of the neck, anxious expression, orthopnea, marked dyspnea, wasting.

*Head.* Complete alopecia, pupils somewhat irregular, react somewhat sluggishly to light, well to accommodation. Two artificial teeth, numerous gold crowns, tongue slightly coated, pharynx slightly reddened.

*Neck.* Right submaxillary gland enlarged, thyroid slightly enlarged.

*Chest.* Negative.

*Lungs.* Dullness to flatness with slightly diminished breath sounds, D8 to D10, left posteriorly; small moist râles at both bases.

*Heart.* Apex in sixth interspace at anterior axillary line, rate 98, no thrill, no enlargement to right; dullness in fifth interspace, 10.5; sixth, 11.2; occasional premature beat, soft low, systolic murmur is heard best in the third interspace to the left of the sternum. A2 is more accentuated than P2. Radial artery is beaded, pulses forceful, blood pressure: right arm, 182 systolic and 118 diastolic; left arm, 190 systolic and 120 diastolic.

*Abdomen.* Liver four and one-half fingers-breadth below the costal margin; fluid wave, free fluid in flanks.

*Genitalia.* Attached to the left spermatic cord, a hard egg-shaped, tender mass is palpable.

*Extremities.* Slight tremor of the fingers; both legs amputated, right stump at junction of middle and lower thirds of thigh, left at junction of upper and middle thirds; both markedly edematous.

*Course.* June 19, 1927. The patient suddenly became cyanotic, dyspneic, respirations 32 per minute, complained of cardiac pain and abdominal distention. The pulse was strong and regular. Edema of hands rapidly developed, loud moist râles were present at both bases with fluid in the left chest and ascites. Respirations were 56 per minute. Blood pressure rose to 232 systolic and 130 diastolic. Patient received morphin and atropin. He became markedly cyanotic, stuporous, irrational, respirations were labored. He died at 3 A.M., June 20, 1927.

*Laboratory Findings.* Red blood cells, 5,400,000; hemoglobin, 92 per cent; white blood cells, 8120; polymorphonuclears, 82 per cent; small lymphocytes, 14 per cent; large lymphocytes, 4 per cent; blood sugar,* 172; blood urea, 19.1; blood Wassermann, negative. Urine: trace of albumin; P.S.P.: 8 + 10 per cent = 18 per cent.

*Electrocardiogram.* L–V–P. P notched in first and second leads; slight peaked notching of Q–R–S in second lead; A–V conduction time −0.18.

*Roentgen Ray.* Fluid at right base; heart enlarged to left.

*Temperature.* 98.6°, on admission, to 96.6° before death.

*Anatomical Diagnosis.* Thromboangiitis (clinical); generalized atherosclerosis, moderate; cardiac hypertrophy and dilatation; surgical amputation lower extremities; *thrombosis of hepatic artery;* thrombosis of left iliac artery; arteriolo- and arteriosclerosis of kidneys; adenoma suprarenal; hydrocele spermatic cord (left); terminal bronchopneumonia.

General appearance and external findings were similar to physical findings. Liver was 2 cm. below the costal margin. Abdomen contained a liter of turbid fluid. There were adhesions between fundus of gall bladder and hepatic flexure of colon. The intestinal coils were moderately distended. Stomach was markedly dilated.

*Heart.* Weighed 550 gm. *Measurements:* Aortic ring, 7 cm.; mitral ring, 10; pulmonic ring, 8.5; tricuspid ring, 12; left ventricular wall, 15 mm.; right ventricular wall 5.8 mm. Heart was markedly enlarged, right side flabby, left ventricle firm. Epicardial surface was thickened, opaque in a small area over the left auricle. Sinuses behind the pulmonic leaflets were markedly dilated and thinned out. There was marked dilatation and slight hypertrophy of the right auricle and ventricle, especially in the region of the pulmonary conus. Left auricle was slightly dilated, endocardium moderately thickened, opaque. Left ventricle was markedly enlarged, firm marked dilatation, moderate hypertrophy. Endocardium showed a few scattered yellowish-white puckerings, up to 1 cm. in diameter. Myocardium was firm, pale.

*Lungs. Right:* All three lobes were voluminous, upper two lobes were soggy. Lower lobes contained scattered irregular nodules of consolidation. On section, there was marked chronic passive congestion throughout with slight edema. In lower lobe scattered areas of early bronchopneumonic consolidation were present. The bronchi were dilated and contained large amounts of mucopurulent material, mucous membrane was purplish. Vessels: All arteries were moderately thickened with numerous atheromatous plaques. Root glands were edematous, enlarged, moderately congested.

* One year before (June 15, 1926, Lebanon Hospital), blood sugar, 104; urea, 20 and Wassermann negative.

*Left:* There was chronic passive congestion. Bronchi, vessels and root glands were similar to those of the right lung.

*Liver.* Weighed 1750 gm. The organ was larger and firmer than average. The capsule was very slightly thickened and wrinkled. On section, architecture was blurred, lobulations were fairly regular, central veins were prominent. The tissue was uniformly pale except for the regions along the borders, where there was a moderate passive congestion. The entire *hepatic artery* was thrombosed by a laminated, partially organized (?), firmly adherent clot which extended into both main right and left branches. The celiac axis, gastric and splenic arteries were markedly thickened but not occluded. The right and left divisions were markedly tortuous, dilated and thickened. The thrombi were traced several centimeters into the depths of the respective lobes. The portal veins were slightly dilated, otherwise negative.

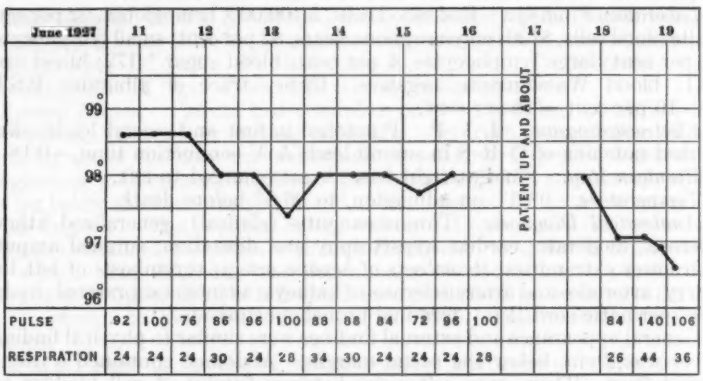


CHART I.—Temperature chart.

*Gall Bladder and Ducts.* No abnormalities.

*Spleen.* Weighed 200 gm. The organ was of average size, firm, capsule was slightly diffusely thickened, smooth. On section, surface was dark red, smooth, nodules were invisible, trabeculæ and vessels were normal.

*Kidneys.* Each weighed 120 gm. *Right:* The capsule stripped fairly easily, leaving a moderately superficial pitted purplish surface. On section, zones were of irregular width, striations were irregular and pyramids purplish. The larger and smaller vessels were markedly thickened. *Left:* Removal of capsule left a smooth pale surface studded with pin-head sized yellowish-white flecks. On section, the organ was strikingly pale, architecture was distorted and throughout the cortical and pyramidal portions there were pin-head and streaked areas of yellowish-white color. The pelves and ureters were negative, vessels were thickened.

*Suprarenals.* Left weighed 10 gm., right weighed 8 gm. There was a cortical adenoma 1.5 cm. in diameter at the upper pole of the left. Otherwise both were similar. Cortices were wider than average, fatty. Medulla was small.

*Neck Organs.* Not obtained.

*Gastrointestinal Tract.* The *stomach* was markedly dilated, mucous membrane was congested and covered with a thick layer of adherent mucus. The *ascending* and *transverse colon* showed marked congestion with small foci of hemorrhage of the mucous membrane. The rest of the tract was negative.

*Pancreas.* Organ was small. On section, there was moderate fatty and fibrous replacement of acinous tissue, islands were small.

*Pelvic Organs.* The *bladder, prostate* and *seminal vesicles* were negative. *Testes:* There was a hydrocele of the left cord, represented by a thick-walled cystic structure filled with fluid. The cyst measured 3 by 2 cm. The *epididymes* were negative.

*Vessels. Aorta:* From the root to the bifurcation there was a diffuse atheromatous involvement showing in places large elevations of translucent watery tissue. Throughout there were parallel linear streaks suggestive of lues. The branches showed similar thickening and parallel puckering. In the terminal portion of the iliac and the proxinal portion of the femoral arteries there was a breaking down occluding thrombus. There were no thrombi in the right iliac artery. The *vena cava* and *tributaries* were negative.

Microscopic Notes. *Heart.* Moderate fatty infiltration of muscle fibers.

*Lung.* Several sections show moderate chronic passive congestion, very slight thickening of intima of smaller vessels and marked thickening of the intima of the larger vessels. In one section, a small vessel shows almost complete obliteration. One section shows a large area of recent bronchopneumonia.

*Liver.* Marked passive congestion with slight degeneration at center of lobules. A large artery is markedly thickened due to proliferation of intima. Sudan III stain shows moderate fatty changes in liver cells. Glycogen stain negative.

*Spleen.* Marked passive congestion, Malpighian bodies are of average size, vessels are moderately thickened and hyalinized.

*Kidneys.* Several sections show a moderate number of glomeruli partially and completely obliterated by hyalinized fibrotic tissue, moderate number of tubules distended and filled with pink-staining homogeneous substance; marked congestion; marked thickening of the intima of the larger and smaller vessels with almost complete obliteration of the lumen in places. Marked small round-cell infiltration throughout and in pelvis.

*Suprarenal.* Marked congestion. Cortical cells pale-staining and contain abundant lipoid. Another section shows a large cortical adenoma 1 by 0.5 cm. in the gross. Vessels show moderate thickening of the intima.

*Pancreas.* Two sections: Two small vessels in one section show complete obliteration of lumen with recanalized thrombi. Both sections show marked fatty replacement of acinar tissue. Islands average. Marked thickening of intima of vessels.

*Prostate.* Average. Marked thickening of the intima of the larger vessels.

*Testis.* Atrophy of tubular elements. Vessels show moderate thickening of intima of vessels.

*Spermatic Cord.* Marked thickening of the intima of the vessels, two of them are partially occluded by organized thrombi. On the free surface, there is a layer of organized granulation tissue.

*Thymus.* Well involuted.

*Stomach.* Slight catarrhal inflammatory reaction of mucous membrane.

*Colon.* Marked congestion.

*Lymph Nodes.* Moderate involution.

*Aorta.* Four sections: Hyalinization and fibrous thickening of intima with areas of cholesterol crystal spaces in several sections, with slight perivascular small round-cell infiltration.

*Vessels.* For pictures and schematic representation see figures and Chart II. *Iliac artery:* Marked thickening of the intima with hyalinization and fibrosis. Unclotted blood in lumen. *Aorta:* Moderate athero-

sclerosis. *Hepatic artery:* Marked atherosclerosis, bland laminated clot. *Left branch:* Slight atherosclerosis, lumen is filled with bland laminated clot and small amounts of blood. *Right branch:* Occluding organized thrombosis.

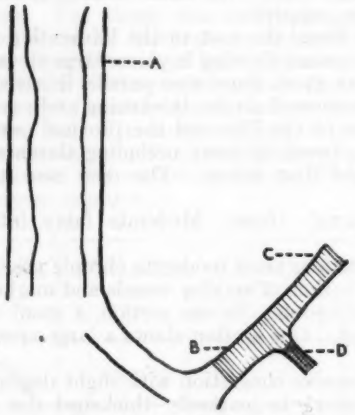


CHART II.—Schematic diagram of hepatic artery and branches. *A*, aorta, moderate atherosclerosis; *B*, main artery, marked atherosclerosis, bland laminated clot; *C*, left branch, slight atherosclerosis, bland clot; *D*, right branch, occluding organized thrombus.

CASE II.—(Städtisches Krankenhaus im Friedrichshain.) A female, aged fifty-four years, was admitted to Ward 15A of the hospital, July 24, 1928, in a moribund condition and died two hours later; on admission, temperature 38° C., pulse 93. History was not obtainable.

**Autopsy** (No. 900; performed July 25, 1928). *External Appearance.* Medium-sized female, elderly appearance, moderately muscular and adipose. Skin and conjunctiva were light lemon-yellow in color.

*Brain.* Basilar vessels showed tiny yellowish-white plaques on intima.

*Abdomen.* On opening the abdominal cavity, slight amount of gas escaped; no fluid was present. Peritoneum smooth and glistening. Firm, white, thin adhesions between the capsule of the spleen and abdominal surface of diaphragm. Firm white adhesions, separated with difficulty from the neighborhood of the distended gall bladder which was the size of a man's fist. Pelvis clear. White, firm adhesions around the tip of the appendix. Fine fibrinous adhesions between intestinal loops.

*Chest.* Pericardium free. Few scattered adhesions of both pleuræ, especially at apex.

*Heart.* Small and soft. Valves and chambers free. Fat infiltration of right ventricle.

*Left Lung.* Pleura smooth except in regions of adhesions. Surface: grayish blue with numerous blackish spotting. At the apex, about the size of an apple, the lung was firm in consistency, airless. On section, this area was slaty-black in appearance—no fluid expressible. Numerous pinhead gray nodules, dry and fragile, were found in this mass. Remainder of lung, dark red in color. Pulmonary vessels wide, walls thin. Lymph nodes at hilum were hard, pea sized.

*Right Lung.* At apex for a distance of about 2 inches in diameter the pleura was thickened.

*Esophagus.* At the height of the tracheal bifurcation, two bean-sized lozenge-shaped traction diverticula were found with few firm pea-sized bifurcation lymph nodes adherent to them.

*Thyroid.* Lateral lobes were 6 cm. long. Organ was firm, brownish red; on section, colloid containing.

*Spleen.* Measured 11 by 9 by 2.5 cm. Smooth grayish blue surface, soft. On section, soft, moist, violet-red pulp scraped away very readily. Markings not made out.

*Appendix.* Lumen of the apex for 3 cm. was replaced by whitish wall.

*Suprarenals and Vessels.* Free.

*Kidneys. Left:* 10 by 5.5 by 2 cm. Cortex and medulla distinct. Cortex, grayish-yellow, markings not distinct. Medulla, deep red, markings plainly visible. *Right:* 11.5 by 6 by 3.5 cm. Similar to left.

*Uterus.* Small, firm. Two small cervical polyps. Small amount of fresh blood in body.

*Pancreas.* Average size. On the surface and around it, numerous scattered small areas of fat necrosis were found. On section, similar areas were found throughout the pancreas.

*Liver.* Measured 25 by 16.5 by 15 cm. and was of average size. The capsule was thin. The lateral 5 inches of the anterior surface of the organ presented a mottled purplish-red appearance, being discolored by this ovoid area which narrowed toward the lower border. Numerous small conglomerate greenish-yellow tiny areas were scattered throughout. The remainder of the right lobe and the entire left lobe were brownish-yellow with a pinkish-red network in them (dilated capillaries). The posterior and inferior surfaces were similar.

On section, the left lobe of the liver and the left quarter of the right lobe were yellowish-brown in color. The markings were indistinct. The area that was purplish-red in color was well demarcated by an irregular wavy line that ran at an angle of about 20 degrees from the coronal section of the midportion of the liver, posteriorly and inferiorly. Roughly, one half was purplish-red in color. The remainder of the cut surface was a yellowish-brown. Irregular moth-eaten yellowish-green areas about 1.5 cm. in diameter and smaller areas were scattered through the purplish area. The walls of these small areas were soggy, smooth in places but for the most part rough and were light to dark green in color. Practically all the large veins were filled with thrombi. Some of these were laminated. The larger arteries were filled with adherent dark-brown clots. The large ducts were wide, the mucous membrane pinkish and slightly thickened.

*Gall Bladder.* About two and one-half times the normal size. The peritoneal surface was covered by a thin adherent fibrinous exudate. On section, it contained about 100 small silvery-faceted stones and thick dark-green fluid. The wall was slightly thickened. The mucosa presented a mottled black and dark-green appearance as if necrotic. A large anthracotic lymph node was present near the neck of the gall bladder.

*Bile Ducts.* Dilated, the walls were slightly thickened with a pinkish-red lining membrane and contained yellowish-brown bile.

*Hepatic Artery.* The entire main artery and branches were free except for the right and left branches as the vessel entered the liver where a laminated dark-brown adherent clot was found. This extended deep into the liver tissue. The clot could not be easily separated from the vessel wall.

*Hepatic Veins.* The right tributary of this vein was filled from its origin in the liver for about 3 cm. by a dark-brown nonadherent clot.

*Portal Vein.* Reddish-brown adherent thrombus originating at the bifurcation and extending into the branches in the liver.

Bacteriologic examination of the spleen revealed Gram-positive bacilli, staphylococci, Bacillus coli, Bacillus proteus and streptococci.

*Anatomical diagnosis:* Cholelithiasis; diphtheritic cholecystitis; thrombosis of the portal vein, hepatic artery and branches of hepatic veins; acute cholangitis with cholangiectasis; cholangiectatic abscesses of liver; hemorrhagic infarct of the liver (large); fat necrosis of the pancreas; infectious splenic tumor; parenchymatous degeneration of heart and kidneys; healed tuberculosis L.U.L.; traction diverticula of esophagus; icterus.

Microscopic Examination. *Heart.* Cells swollen and granular, moderate brown atrophy, moderate fatty changes in the musculature.

*Liver.* Moderate congestion, granular degeneration and fatty changes in the regions beyond the infarct. The infarcted region is limited by hemorrhagic and leukocytic areas. In places periportally, larger and smaller areas of necrosis with extensive leukocytic infiltration are found. The bile ducts show desquamation of mucous membrane and in some areas regeneration of the bile ducts is present. In places, the smaller vessels are filled with leukocytes and the endothelium is invaded by them.

*Gall Bladder.* Bluish thick layer of fibrin on an almost absent mucous membrane. Slight leukocyte reaction in this fibrotic region and in the wall of the gall bladder.

*Portal Vein.* Filled with a network of fibrin engulfing numerous degenerated leukocytes with red blood cells at the periphery. The adjacent tissue and wall of vessel are markedly infiltrated by red blood cells and leukocytes. The connective tissue and musculature contain pale pink-staining cytoplasm, with moderate pyknotic changes in the nuclei.

*Hepatic Artery.* Filled with fibrin, red blood cells, numerous degenerated leukocytes and a medium-sized area of canalization. The wall is infiltrated with leukocytes. The vasa vasorum are congested.

*Pancreas.* Larger and smaller well demarcated areas of fat necrosis are found.

*Kidney.* Capsule is thin. Tubules and glomeruli show marked replacement of the protoplasm by a granular pink-staining material. In places there are ghosts of glomeruli. The tubules are filled with a pale pink-staining material. Moderate fresh calcium deposits are present in the walls of some of the tubules. The smaller and larger vessel walls are moderately thickened and filled with pink-staining amorphous material.

**Discussion.** Lesions of the hepatic artery are often overlooked by pathologists who do not open the vessel for its entire length as a routine. This may partly account for the rarity of hepatic artery thrombosis in the literature.

These rather rare and unusual cases reopen the subject of lesions of the hepatic artery and the effects of its ligation in animals and in man. This has been a very fertile field for physiologists since Simon de Metz,[10] in 1828, first ligated the hepatic artery in pigeons. Cohnheim and Litten[11] and Doyon and Dufourt[12] produced experimental thrombosis of the hepatic artery with subsequent necrosis of the liver by tying off the main artery and its branches. Segall,[13] in an extensive dissertation on the liver circulation, reviews the literature and stresses the importance of proper surgical ligation. He reached the conclusion that the hepatic artery might be ligated in the human in its main stem proximal to the gastric artery without notable effects on the nutrition of the liver. Ligation distal to the gastric artery when the hepatic artery is previously healthy, results in more or less extensive necrosis and eventual total necrosis must be feared. Necrosis of the liver occurs when there are no accessory hepatic arteries, no unusually large collaterals, or from sudden total

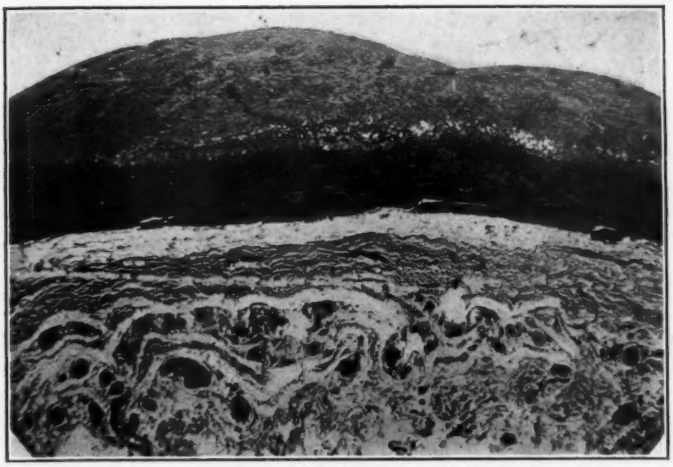

FIG. 1.—Aorta of Case I showing atheromatosis.

FIG. 2.—Hepatic artery of Case I showing atherosclerosis and occluding thrombus.

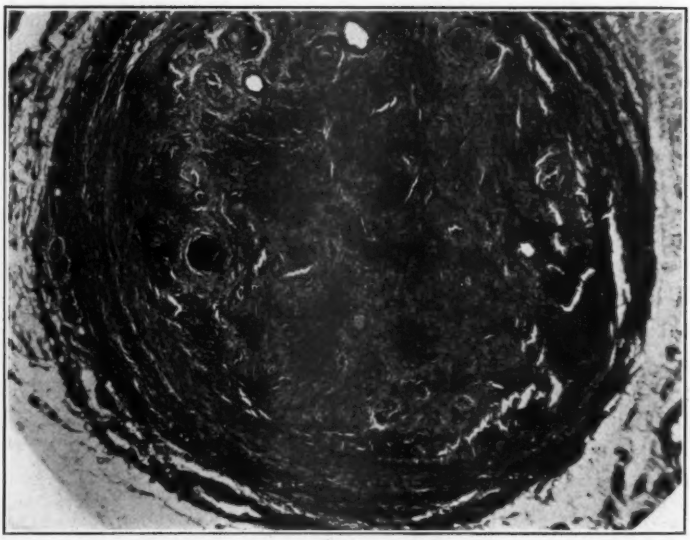

FIG. 3.—Right branch of the hepatic artery of Case I showing organized thrombus.

obliteration of the flow. Arterial blood is essential to the life of the liver substance.

Nicoletti[14] offers the explanation that the broad junction of the hepatic lobes with each other in man makes it possible to ligate separately the final branches of the hepatic artery, but Narath and Thole[15] believe the dangers of necrosis are too great to permit separate ligation of these branches.

Narath[16] has reported 20 cases of ligation of the hepatic artery or its branches. Two cases (Socin and Salzer) died within seven hours and showed no necrosis of the liver at autopsy. Two cases had the portal vein as well as the hepatic artery ligated (Sprengel, Guibe and Herrenschmidt) with necrosis of the liver and death. Kehr, in 1903, ligated the hepatic artery for aneurysm of that vessel, the first time it has been reported with recovery. He ligated the main branch or its branches on three further occasions with similar results. Tuffier, ligating the hepatic artery for aneurysm in a man, aged seventy-two years, found necrosis of the liver at autopsy. Wendell ligated the vessel distal to the gastric branch with resulting total necrosis of the liver and death in thirty-six hours. In three cases the right or left branch (Bakes, Allessandri, Palacio) was ligated with recovery. Narath, Wilms and Tichow did the same operation and found necrosis of the lobe of liver at autopsy. Haberer and Wendell removed a lobe of the liver after tying off the corresponding arterial branch with favorable results. Klose carried out the same procedure and attributed the death to endocarditis.

Kaeding[17] ligated the hepatic artery for aneurysm with a favorable result. Behrend[18] tied the hepatic artery on both sides in a boy, aged six years, who had been run over. No autopsy was performed after the boy died with a clinical picture resembling acute yellow atrophy. Anderson[19] ligated a branch of the vessel for aneurysm with uneventful recovery from this operation. Smith[20] tied off the artery for bleeding in an hepatic operation, the patient recovering. Hofmeister[21] ligated the artery at the gastric branch for hemorrhage with a similar experience but Holst,[22] in a gastric operation, lost the patient with necrosis of the left lobe.

These experiences do not lend themselves to very definite conclusions. However, ligation seems to be the best method of treatment for aneurysm of the hepatic artery. A well developed collateral circulation occurs in this or any other similar type of injury of long standing and might allow ligation at any portion of the vessel. When one branch is ligated, removal of the corresponding lobe, especially if lesions are found, is advisable. In extensive adhesions around the liver, the collateral circulation might be sufficient to allow ligation of the artery near the celiac axis. Bourdenko[23] has utilized this fact in animal experiments by suturing the omentum to the liver, thereby obtaining a collateral circulation and then after some days, tying the hepatica propria. The results are by no means conclusive, but he believes that the necroses are

less extensive. Villandre[24] attempted to avoid the danger by slowly constricting the artery before ligation.

Narath and Steckelmacher[25] studied histologic changes in the liver after ligation of the hepatic artery. Among the most important findings are periacinar connective-tissue proliferation and cyst formation, both described by Janson[26] also. It must be emphasized that this formation of connective tissue has nothing in common with true cirrhosis of the liver (Rost[27]). Rabinovitsch[28] recently showed that the arteria hepatica propria anastomoses regularly in the transverse fissure with the accessory artery branching off from the arteria gastrica sinistra or the arteria mesenterica superior, adding another link in the anastomatic chain.

**Summary.** Two cases of thrombosis of the hepatic artery are reported. In one, an acute case, probably secondary to biliary-tract infection, there was involvement of the portal and hepatic veins, a hemorrhagic infarct in the liver and the hepatic artery showed a thrombus at its bifurcation extending into the liver. In the other, a more chronic case, probably of atherosclerotic origin in a man with thromboangiitis obliterans, the main artery was involved, no infarct was present. The patient probably did not die from this condition.

The clinical and experimental evidence would suggest that the degree of liver injury following occlusion of the hepatic artery depends in part upon the site of the occlusion and in part upon the extent of the collateral circulation.

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# THE MEDICAL OR INJECTION TREATMENT OF VARICOSE VEINS.*

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The idea of obliterating varicose veins by the injection of drugs occurred to Provatz in 1851.[1] Such blood coagulating solutions as perchlorid of iron, alcohol, tincture of iodin and Pregl's (isotonic iodin) solution were first tried, with resultant reactions, infections and fatalities. De Lore,[2] in 1894, showed that success was due to the reaction of the drug on the intima and not the coagulation of the blood. In 1911 P. Linser[3] introduced 1 per cent mercury bichlorid, and with his brother, K. Linser,[4] changed to 20 per cent sodium chlorid solution in 1923, which they found safer because less toxic. About this time Sicard,[5] in Paris, used sodium salicylate, while Kausch and Nobl,[6] in Vienna, preferred invert sugar solutions.

After fifteen years' experience in the treatment of 48,000 cases it is now the accepted form of treatment in most of the European clinics. In this country results reported by Hayes,[7] McPheeters,[8] Bratrud,[9] de Takats,[10] Schussler,[11] Kilbourne[12] and the author[13] prophesy its increasing popularity. They prefer the injection method to surgery because there is less cost to the patient, less pain, better cosmetic results, recurrences are less frequent, danger of embolism is less and the patient is ambulatory.

In a survey of 4607 operative cases, Kilbourne[12] finds 1 death in each 250. In 53,000 cases treated by the injection method, McPheeters[14] found 11 fatal cases, to which Kilbourne[12] adds 2 more. This is about 1 in 4000 cases. Recurrences after operation average about 30 per cent compared with 7 per cent by the injection method. Some men take a half-way position, using surgical excision of certain varices with injection of the remainder. I can see no good reason for adding the dangers of surgery when the injection method alone can be used successfully in all kinds of varices.

**Action of Sclerosing Drugs.** The delayed acceptance of this method of treatment by the medical profession has been due to fear of emboli. Animal experiments by Doerfell,[15] Regard[16] and Bazelis,[17] and removal of sclerosed veins in humans by de Takats[10] and V. Meisen,[18] have shown that an adherent, fibrotic clot is formed in the veins injected with sclerosing solutions. The irritating action of the latter causes a destruction of the intima followed by a trabecular deposit of fibrin and blood platelets resulting in an adherent, dense, fibrous clot, often extending into offshooting branches, in which organization with connective-tissue formation proceeds and

* Read before the section of Pharmacology and Therapeutics at the last meeting of the American Medical Association at Portland.

progressive retraction takes place, finally resulting in a thin, fibrous strand in which only a few muscle fibers are demonstrable. This explains the paucity of emboli. The mechanism of the action of obliterating injections and the pathologic changes in the veins have previously been described by Forestier[19] and the author.[13]

**Nature of Sclerosing Drugs.** Various drugs are being used by various men to accomplish the same result, namely, a hard, firm, permanent fibrosis of the vein. I will briefly summarize the characteristics of the most popular ones.

*Bichlorid of mercury*, the first drug used to obliterate veins, is little used now because of its toxicity and severe sloughing if some is accidentally injected into the tissues. Only one injection can be given at a time and the small amount injected results in only a small sclerosis, thus requiring many injections; 1 cc. of a 1 per cent solution is the maximum amount that can be given at one time. The same objections apply to red mercury iodid and mercury cyanid.

*Sodium chlorid* is still used routinely in some clinics here and abroad, but most men have given it up in their private practices because of the severe painful cramps immediately following injection, severe sloughing if injected outside a vein and frequency of "perivenitis." I use it occasionally in "intima resistant" cases (which I described in a former paper), giving 5 to 10 cc. of a 20 to 35 per cent aqueous solution. Linser and others find that multiple injections requiring larger amounts increases the danger of embolism.

*Sodium salicylate*, introduced by Sicard,[5] is used quite extensively in France by Forestier[19] and others. The usual amount given is 5 to 10 cc. of the 20 per cent or 2 to 6 cc. of the 25 to 40 per cent aqueous solution. I have found that a moderate degree of a burning pain lasting thirty to sixty seconds occurs immediately after such an injection. If less than 5 cc. of the 20 per cent is injected very little pain is experienced, according to Bratrud.[9] Of course, a slough is produced if any amount is injected outside the vein, especially in strengths greater than 20 per cent. If larger amounts or a stronger solution is used the pain is greatly increased and complained of by most patients. I prefer sodium salicylate in strengths of 20 to 35 per cent in cases where the intima resists the irritating action of repeated injections of invert sugar preparations, given with careful technique. Sclerosis is obtained in a high percentage of cases after the first injection with the 25 to 35 per cent strengths.

*Sugar solutions* have been used since 1923 in the forms of *glucose* and *invert sugar*. They cause little or no pain (slight muscle cramps or tight feeling in leg in 30 per cent in author's series) are nontoxic and result only in a painful, indurated area *without sloughing* if injected *outside* of a vein, which is relieved in a few days by frequent applications of wet heat. Painful perivenitis is less frequent than

TABLE I.—ANALYSIS OF VARIOUS FORMS OF TREATMENT.

| Drugs used. | Mercuric chlorid. | | Sodium chlorid. | | | Sodium salicylate. | | | | Invert sugar. | | | Invert sugar and sod. salicyl. | | Calorose. | Glucose. | Quinin-urethane. |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Concentration used, per cent | 1 | 0.5 | 20 | 25 | 30–40 | 20 | 20 | 25 | 35 | 50 | 60 | 70 | 50–60–70 | | 40–60 | 50 | |
| Usual dose, cc. | 1 | 2 | 10 | 5 | 5 | 2–5 | 5–10 | 3–6 | 2–5 | 10–20 | 10–20 | 5–10 | 5–10–15 | 5–10 | 10–20 | 10–20 | 1–2 |
| Toxicity | VS | VS | s | m | m | s | s | s | s | o | o | o | s | s | o | o | m |
| Cramps or pain | o | o | S | VS | VS | s | m | S | VS | o | s | s | o | s | s | s | m |
| Action on intima | m | s | m | S | VS | m | m | S | VS | m | S | S | S | VS | m | m | m–S |
| Efficiency, per cent | 70 | 60 | 70 | 90 | 97 | 70 | 78 | 90 | 97 | 78 | 85 | 90 | 80 | 93 | 60–70 | 60 | 70 |
| Slough | S | S | S | S | S | m | m | S | S | o | o | s | s | s | o | o | S |
| Periphlebitis, per cent | 5 | 5 | 15 | 20 | 25 | 5 | 5 | 10 | 12 | 3 | 5 | 8 | 3 | 5 | 5–8 | 5 | |
| Indications | Diabetes intima; resistant cases | | Diabetes intima; resistant cases; routine ? | | | Diabetes intima; resistant cases; routine | | | | Routine | | | Routine | | Routine | Routine | Small veins; selected cases. |
| Contraindications | Nephritis; P.O. cases; pregnancy; art.scler.; feathery veins | | Neurotics; P.O. cases; feathery veins | | | Idiosyncrasy | | | | Untreated diabetes | | | Untreated diabetes; idiosyncrasy | | Untreated diabetes | Untreated diabetes | Pregn.; idiosyncrasy. |

o, none; s, slight; m, moderate; S, strong or severe; VS, very strong or severe.

with the more caustic solutions. I have noted that formation of the thrombus may proceed more slowly with sugar solutions, but, finally, firm organization results. Glucose, because of its high viscosity in strengths over 50 per cent requires such a large needle that it is impractical except for larger veins. In my hands, a comparatively low percentage of sclerosis obtained after the first injection. De Takats[10] and others prefer it as a routine. Invert sugar is the natural chemical combination of equal parts of dextrose and levulose with 3 to 5 per cent sucrose resulting from the hydrolysis of cane sugar. Nobl[6] has led the way in popularizing its use. He has reported great success in over 10,000 injections without a fatality. It is dispensed in Europe under the name of calorose, and in this country as invertose or invert sugar, in 10-cc sterile ampules ready for injection; the calorose in strengths of 40 and 50 per cent, the invert sugar and invertose in 50, 60 and 70 per cent. Its decreased viscosity compared with glucose is its chief advantage over the latter, allowing it to be easily injected in strengths of 60 to 70 per cent through a 20-gauge needle, thus resulting in a higher percentage of successful sclerosis after single injections in small as well as large varices. I used 50 to 60 per cent invertose routinely in my first 450 cases, with successful sclerosis after initial injections in 85 per cent, careful technique being observed. In the remaining 15 per cent repeated injections of 60 to 70 per cent invertose, sodium chlorid or sodium salicylate, 25 to 35 per cent, gave sclerosis. The fact that sugar preparations are "just sugar," nontoxic and almost painless, make them popular with the patients.

During the past three months I have been using a new preparation (invertose compound). It is a combination of 50 to 60 per cent invert sugar with 5 to 12.5 per cent sodium salicylate. I have now used it in about 100 cases—600 to 700 injections—and am quite enthusiastic about it. The sodium salicylate increases the irritant action on the intima, resulting in a firmer and higher percentage of sclerosis, without increase in pain or danger of necrosis if small amounts are injected outside the vein. The sodium salicylate also decreases the viscosity, allowing stronger solutions (60 to 70 per cent) to be injected through smaller needles.

*Quinin-urethane* solution, in doses of 2 cc., was advocated by Genevrier[20] and Douthwaite.[21] Immediately upon injecting into the vein, a severe prickly burning sensation is felt for an instant at the point of injection. Because of its short duration, the pain is usually not objected to. It is toxic, especially to patients sensitive to quinin and pregnant women. Kilbourne[12] reports 5 cc. killing a 7½-pound rabbit. Sclerosis is not certain. I find it limited almost to small "pick-up" veins remaining after a general closure.

*Metaphen* has been recommended by Schussler[11] for small veins. I have had no experience with it.

*Varicophytin* is a European product of sodium chlorid combined with an opiate to relieve the pain caused by the former. I have been unable to obtain any of it myself or to find any reports of its use in the literature.

Forestier[19] has rightfully stated that each varix has its own reactive power which is independent of the degree of dilatation. The physician must decide in each case the concentration of the sclerosing agent and use the weakest solution that will prove efficient.

**Technique of Injection.** This varies somewhat according to the location, size, nature of varices, equipment of physician and solution used. I mention first some general rules which I have found from experience to be helpful. Large varices, especially if long, should first be injected near their lowest point and so closed upward, but never injected higher than the middle of the thigh. Clumps, plexes or masses of large varices usually found over the calf of the leg are prone to develop perivenitis, so strong caustic solutions should be avoided, especially in large amounts. Sugar solutions are safest. I use an iron ring, 2 or 3 inches in diameter, pressed firmly against the leg to keep the solutions from escaping.

It is hard to prophesy how a vein will sclerose, as some large veins close extensively from a weak injection, while some small veins may need repeated injections of increasing concentration at the same point. It is safest to start with weak solutions.

In case of ulcers, always inject their feeders first, inserting needle at point well away from the inflamed infected area. Feeders may enter ulcer area from any angle, and frequently run under the ulcer.

In case of very large varices, I add 2 or 3 minims of sterile 1 to 1000 adrenalin solution to 20 cc. of the stronger invert sugar preparations (60 to 70 per cent) to cause contraction of the vein, and then apply elastic bandage to keep them collapsed. This hastens cosmetic results.

It is safest not to give more than two injections at a sitting, that is, one in each leg. I consider 40 cc. (two 20-cc. doses) of any of the invert sugar solutions (60 to 70 per cent), or 20 cc. of the invert sugar and sodium salicylate solution, an advisable *maximal* dose. The literature shows that many of the cases of reported emboli followed where many injections were given at one sitting.

*Nonsclerosis* is due to poor technique or increased resistance of the intima to the irritating effects of the sclerosing agent, an individual characteristic.

Expect a slough in all cases where extravenal accidental injection has occurred, except when sugar solutions are used, and dilute solution in the tissues liberally by injecting normal saline and massage area five to ten minutes.

Test patency of deep veins by Trendelenburg and Pratt methods before injecting in suspicious cases. Never inject where deep veins are closed.

Advisability of treatment and prognosis should be guarded in cases of hard chronic edema or elephantiasis.

Good results have been obtained by various men using somewhat different technique. The main thing is to get the solution in contact with the intima of the varix with the least dilution by the blood. While the patient stands erect so as to distend his veins, the point of injection is selected and marked with 1 per cent mercurochrome. A rubber tourniquet is now applied well above this point. The patient then lies prone on a table with an adjustable leg-rest. The skin is sterilized as for any intravenous injection. A sharp sterile needle, 18- to 24-gauge, according to size of varix, attached to a sterile glass Luer syringe, filled with the solution at body temperature, is carefully inserted into the marked varix. Blood is aspirated to be sure the needle is well within the vein. The tourniquet is now removed, relieving the distention. The assistant with index fingers now carefully "milks" the remaining blood from a section of the varix for a distance of a few centimeters above and below the needle, being careful not to disturb the latter. After assuring oneself that the needle is still in the vein, inject the solution rapidly enough to produce slight distention. The amount required will vary from 5 to 20 cc. (in case of invert sugar preparations), depending on size of varix. Keep fingers of assistant and needle in place for five minutes. Apply sterile pressure gauze pad with adhesive strips where needle was removed. If veins are large and prominent apply a larger nonsterile pressure pad over section of vein expected to become sclerosed and hold in place by rubber elastic bandage from ankle to thigh, kept on for one to two weeks, and only removed during the time of subsequent injections which can be given bi- or tri-weekly. This allows veins to become sclerosed in a collapsed condition, giving quicker cosmetic result. Instruct the patient to get up and go about duties as usual to attain best results.

Usually twenty-four to forty-eight hours after an injection one of the following results will occur: (1) No sclerosis; (2) only thickening of vein wall without obliteration of the lumen; (3) complete sclerosis and obliteration of vein lumen resulting in a tender fibrous cord; (4) same as (3), with "perivenitis" (described later). In the case of (1) and (2) repeated injections at some point with increasing concentration of solutions must be made.

**Observations and Results in Five Hundred Cases.** The following is a brief summary of my observations and results in 500 cases with over 5000 injections, occurring in private practice since February, 1927. This is a considerable increase in the number of injections per patient over our preliminary report. The ages varied from seventeen to seventy-nine years, most of whom were females. A careful history was taken on all the cases, especially with regard to local symptoms, previous internal or external phlebitis and con-

FIG. 1*a*.—Mr. H. A. Before treatment.

FIG. 2*a*.—Mr. W. W. Before treatment.

FIG. 3*a*.—Mr. S. S. Before treatment.

FIG. 1*b*.—Mr. H. A. After treatment. (Two months).

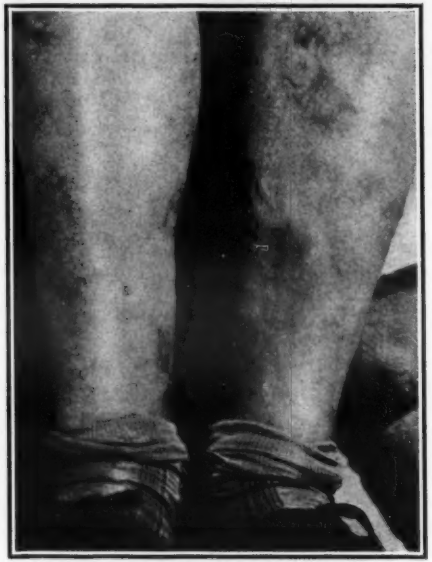

FIG. 2*b*.—Mr. W. W. After treatment. (Four months).

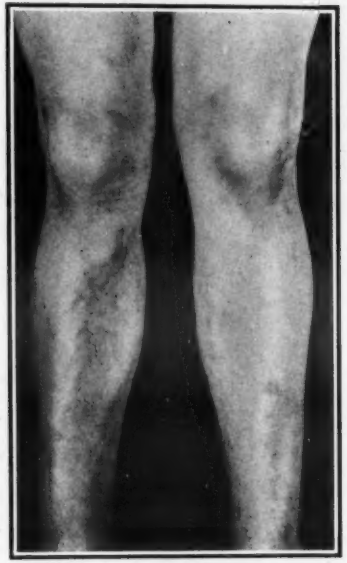

FIG. 3*b*.—Mr. S. S. After treatment. (Six months).

stitutional diseases. A urinalysis was done on all cases, and a physical examination when indicated. Whenever a previous internal phlebitis was ascertained or suspected, a Trendelenburg test and that advocated by J. P. Pratt for patency of the deep veins was done. The latter test consists of closing off the circulation in the superficial veins by firmly applying an elastic or Ace bandage from ankle to thigh; then have the patient walk for about a mile. If the deep veins are blocked then all venous circulation is cut off and severe pain will result. If the patient returns in comfort the deep veins must be open. I prefer this test and believe it to be reliable.

The chief complaints were edema, dull aching pains or severe periodical cramps, heaviness of legs, cold feet, ulcers, phlebitis, subcutaneous hemorrhages, rheumatic-like pains about knees or ankles, eczema and periostitis. When *disturbed arterial circulation* or *other diseases*, such as cardiac decompensation, *were not* an added factor, these symptoms disappeared on closure of the varices. Elderly patients, especially, spoke of their legs feeling "twenty years lighter." (Figs. 2*a*, 2*b*.)

Thirty per cent of the patients gave a history of varicosities in one or both of the parents or grandparents, pointing toward a hereditary etiological factor. Time will not allow further discussion of the question of etiology.

Twenty-six per cent of the patients had the veins treated for cosmetic reasons. Results in these cases were most gratifying. (Figs. 3*a*, 3*b*.)

Thirty-five cases showed ulcers. Infective and luetic causes being ruled out, these ulcers showed varices as their only cause. The most common locations were about the malleoli, as this is the source of saphena magna and parva, and the base of the stagnant venous column. Varicose ulcers always have a varicose vein extending into base from above, lateral or even below, which "feeds" it, and whose closure results in permanent healing. (Figs. 1*a*, 1*b*.) Skin grafts may be used in very large ulcers after wet packs of 1 to 4000 mercury cyanid solution have cleaned up any infection. Application of pressure to the ulcer by an ordinary rubber bath sponge and rubber elastic bandage, as suggested by Nobl,[22] is a great aid and gives almost miraculous rapidity of healing. Unna's paste boot is often a great asset, especially if a chronic obstructive lymphangitis exists, and can be used to advantage for support several weeks after ulcers are healed. In cases of marked edema it is best to examine after a preliminary bed-rest period to reduce the swelling, when the true location and extent of the varices can be determined.

Five cases showing phlebitis of the superficial veins were treated in the usual manner. No injections were deemed advisable for *at least six months* after the acute inflammation had subsided.

Eczema must be treated as usual in addition to closing the varices.

Ten cases of apparent chronic obstructive lymphangitis were encountered. They were carefully studied, injecting only varices definitely responsible for some of the edema, and advising the usual supportive measures (Unna's paste boot—elastic stockings or bandages). Prognosis was very guarded.

Serious complicating conditions, such as diabetes, nephritis, hypertension with decompensating heart and so forth, should be treated first and injections given later, if at all, depending on improvement in general condition.

Painful varices below lower one-third of thigh may be treated in pregnant women in the early months with comparative safety, sugar solutions preferred.

One case of varices in legs was cured by removing a large ovarian cyst.

Eight cases were refused injection treatment because of complications already mentioned.

Eleven cases previously operated upon were injected successfully. I warn against the use of the more caustic solutions in these cases as the recurrent veins often have abnormal intimæ.

No embolisms were observed. Three severe sloughs occurred (2 with chlorid of sodium, 20 per cent, and 1 with 1 per cent chlorid of mercury) due to extravascular accidental injection. Surgical excision of slough was done in 1 case with good result.

Twenty-five times moderate to severe periphlebitis followed injections. This is a painful, red swelling along the course of the sclerosed vein, and may involve the entire saphena magna or parva. I believe it to be due to using too caustic solutions on a supersensitive intima, so I now always first try 5 to 10 cc. of a 50 per cent invert sugar preparation to pick up these types. The best treatment is rest and hot wet packs. All veins of any size are naturally somewhat tender for a few days after closure. If closure is extensive this soreness is increased in area and time of course.

Recanalization and return of some of the varices occurred in about 5 per cent after one or two years. These were easily closed again, but more caustic solutions were usually necessary. Improvements in technique and more thoroughly extensive original treatment may reduce this figure.

Based on a plain question to the patients, 98 per cent stated they were satisfied with their results.

**Summary.** 1. The injection method of treating varicose veins, although comparatively new in this country, is well established and has been widely used in Europe for the past ten years.

2. It is safer, cheaper, less painful and more permanent than surgery.

3. Of the various sclerosing agents, sugar solutions, especially

preparations of invert sugar, are safest for routine use, and best for beginners.

4. A careful technique must be worked out in order to bring the sclerosing solution in contact with the intima with the least possible dilution for five minutes.

5. "Intima resistant" cases occasionally occur, and here the more caustic solutions can be used to advantage.

6. A survey of experience and results in 500 cases with over five thousand injections points to the desirability and an increasing acceptance of this method.

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# BLOOD REGENERATION IN SEVERE ANEMIA.*

## XXI. A Liver Fraction Potent in Anemia Due to Hemorrhage.

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and

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This paper deals with a liver fraction which weighs but 3 per cent of the original whole liver yet contains 65 to 75 per cent of the potency of whole liver, as measured by new hemoglobin production in long-continued anemia in standardized dogs. The data here presented deal only with the simplest form of experimental anemia due to bleeding, but it is at least probable that this liver fraction is potent in certain types of human anemia. Observations made in various medical clinics must decide what usefulness it may have in human anemia. The secondary anemia fraction as prepared for this work is palatable and can be ingested in large amounts without any clinical disturbance.

In 1920, Whipple, Robbins and Hooper[11] reported that liver feeding had a very favorable influence on the production of hemoglobin and red cells in dogs during short anemia periods. Since that time Robbins and Whipple have shown that liver feeding has an extraordinary effect on hemoglobin and red-cell production in severe long-continued anemia due to hemorrhage in dogs. During this considerable period Whipple and Robbins have tested a great variety of liver fractions and extractives. Some of these experiments were reported three years ago.[9] More recently with the coöperation of Dr. Sperry and Mr. Elden of the Department of Biochemistry, we have reported[4] a considerable series of liver fractions and extracts which contained much of the potency of the whole liver as measured by new hemoglobin production in severe experimental anemia.

That more than one factor is concerned in this favorable reaction to liver and other food factors is obvious from some earlier experiments[1] in this laboratory which show that the inorganic ash of liver, kidney and apricots is potent in this type of secondary anemia. It was shown that the liver and kidney ash contained about half the potency of whole organs. Probably the contained iron is responsible

* This work has been aided by a National Live Stock and Meat Board Fellowship of the National Research Council. We are indebted to the Rochester Packing Company for a liberal supply of certain meat products.

† Mr. Walden is a member of the research laboratory staff of Eli Lilly and Company.

for a considerable portion of this favorable reaction noted with organ ash.

Recently a liver fraction known to be fully potent in human pernicious anemia (Liver Extract No. 343 N.N.R. prepared by Eli Lilly and Company) has been tested in this type of secondary anemia. It was found by Robbins and Whipple[3] that this pernicious anemia liver fraction contained not over 10 to 20 per cent of the potency of whole liver for the production of new hemoglobin in severe secondary anemia.

Ever since it was firmly established that liver and kidney were rich in materials which contributed so effectively to the production of new hemoglobin and red cells, we have had a logical interest in all fractions obtained from liver or kidney. With ordinary laboratory facilities the production of liver fractions in sufficient amounts to permit of their standardization in dogs is a very difficult task. It was obvious that commercial laboratories could do certain work with great advantage over the school laboratory. Dr. Clowes and Mr. Walden became interested in our problems and offered the facilities of Eli Lilly and Company's Research Laboratories. These laboratories were engaged in the commercial preparation of a liver fraction (No. 343 N.N.R.) potent in pernicious anemia. The results of our work with liver fractions[4] were carefully studied and with this knowledge it was decided to test some liver fractions which were already at hand in the Eli Lilly Laboratories in sufficient amounts for work with anemic dogs.

It is obvious that further purification with study of the various substances contained in the secondary anemia liver fraction will give interesting information. We hope to report on this subject from time to time.

**Methods.** The general methods used in these experiments have been described in sufficient detail in the first,[7] fifth[8] and sixteenth[10] papers of this series. The standard bread used in all control periods and elsewhere as indicated is described as to ingredients and preparation. This bread contains wheat flour, starch, bran, sugar, cod-liver oil, canned tomatoes, canned salmon, yeast and a salt mixture. Bread (S) which contains a little salmon was used in all the experiments here recorded. This bread is a complete diet for an adult dog and will maintain a dog in health for long periods of time, if not indefinitely. This ration keeps the hemoglobin production at a very low level, the average being close to 1 to 3 gm. of hemoglobin per week period over and above the unknown maintenance factor. There are individual differences and some dogs are constantly high in hemoglobin production on the basal rations as well as other diets. The *hemoglobin index* in these papers is a figure obtained by dividing the hemoglobin per cent by the red-cell hematocrit in per cent. We believe this figure gives information of value as to the saturation of the red-cell stroma with hemoglobin.

It is important to remember that these standard dogs are in a condition of sustained anemia (40 to 50 per cent hemoglobin) month after month, year after year. Some of the dogs have been *continuously anemic*, as indicated for four to five years, and are reacting quantitatively to various specific diet intakes in the fourth year as they did in the first year. The experiments given in the tables are taken out of the dogs' experimental history, which is continuous. The figures given represent the observations made at the *end of any given week*, so that hemoglobin figures noted for the first week of any feeding represent the production of hemoglobin due to seven days' feeding of that diet as indicated.

The *reserve storage of hemoglobin factors* is another important point which bears on the interpretation of results. It is surprising to observe how difficult it may be to exhaust this emergency reserve in the healthy dog. We have made it a rule to produce our experimental anemia slowly over a two- or three-week period and to maintain this anemia for two or three months on the standard bread diet to insure the exhaustion of this reserve. During this period as much as 250 to 350 gm. of hemoglobin may be removed by bleeding, representing a tremendous reserve which can scarcely be stored as finished red blood cells. This reserve is probably stored as intermediates which on demand can be combined to form the finished blood hemoglobin. After this period the dog will react with a small and constant hemoglobin output to the standard bread diet and will react uniformly to various diet factors as given in preceding papers.

*Hemoglobin production*, due to any given diet period, is calculated as follows: The hemoglobin level at the end of the fore period or last bread-control week is compared with the hemoglobin level at the end of the after period. If these hemoglobin levels coincide within 2 or 3 per cent no correction is needed, but if the figures are 3 or more per cent apart we correct for this difference in hemoglobin level. As calculated above, a 10-kilo dog has in circulation about 55 gm. hemoglobin at a hemoglobin level of 50 per cent. Therefore we allow a gram of hemoglobin for each per cent difference of level. For example a dog shows a 50 per cent hemoglobin level at the end of the fore period but in the after period is bled slightly too much, which reduces his level to 43 per cent. Obviously we cannot attribute this 7 gm. of hemoglobin to the given diet but to the overbleeding. We deduct this 7 gm. from the tabulated figures to give a correct figure for hemoglobin production on the given diet. Experience shows that this calculation gives an accurate approximation of the actual findings when known amounts of hemoglobin are abstracted from these anemic dogs.

The total hemoglobin production due to any given diet is readily calculated from the tables. The control bread periods show 1.5± gm. hemoglobin production each week. This amount of

hemoglobin is removed for the routine determination of blood volume and hematocrit and some dogs will produce a little more than this amount of hemoglobin per week as the control level. The average value must be very close to 2 gm. per week in our large colony. We deduct this 2 gm. from each week's output above this figure and this includes the two weeks' feeding period plus the two or three weeks after control period. It has been amply proven[2] that on a favorable diet a dog stores substances which later, during the unfavorable control diet or after period, will be turned into hemoglobin and appear often in considerable amounts above the control level. This hemoglobin production of the after period obviously is due to the favorable diet or drug and is added to the hemoglobin production of the actual diet period. There is always more or less lag between the start of a favorable diet period and the rise in the curve of the hemoglobin production. That there is a lag in the fall of the hemoglobin production after any favorable diet period is not surprising. We may choose to explain this lag as due to the complicated internal metabolism of hemoglobin which must be built up from a variety of building stones present in the intestinal contents or stored in the body.

The secondary anemia fraction was prepared as follows: Fresh hog livers were finely ground into water containing dilute sulphuric acid. The mixture was then heated to 80° to 85° C. and filtered. The filtrate was evaporated in vacuo to a thick syrup and precipitated with 70 per cent alcohol. The portion insoluble in 70 per cent alcohol was dried and designated the secondary anemia fraction. This represents 3 per cent the weight of the whole liver or about 10 per cent of the dried liver weight.

The ashing was carried out in a muffle type of furnace using gas as fuel. A quantity of the secondary anemia liver fraction was placed in evaporating dishes and the temperature gradually raised over a period of about two hours to 1200° to 1300° F., held at this temperature for three hours and allowed to cool, requiring about twelve to fifteen hours. Under the above condition an easily powdered light-colored ash was obtained with practically no loss due to fusion.

**Experimental Observations.** When one works with fractions obtained from a fresh organ and attempts to extract a potent factor from a mixture rich in protein it is usually found that the residue contains a sizeable portion of the substance under investigation.[4] Moreover when a variety of fractions are made from a single lot of organ "Brei," it is not infrequent for the activity of the individual fractions to exceed the total activity of the original "Brei." This may be due to inaccuracy of the methods of testing the active principle or it may be due to some changes effected in the original mixture by the chemical processes—in other words the method of preparation may unlock substances which are held in the protein

matrix of the original organ mixture. These points are illustrated in Tables 211 and 212.

TABLE 211. — POTENCY OF LIVER FRACTIONS IN EXPERIMENTAL ANEMIA.

OUTPUT OF HEMOGLOBIN GIVEN IN GRAMS PER TWO WEEKS' FEEDING.

| Dog No. | Secondary anemia fraction. | | Pernicious anemia fraction. | | Residue. | |
|---|---|---|---|---|---|---|
| | Hemoglobin produced 2 weeks, gm. | Liver equivalent daily, gm. | Hemoglobin produced 2 weeks, gm. | Liver equivalent daily, gm. | Hemoglobin produced 2 weeks, gm. | Liver equivalent daily, gm. |
| 23–1 | 62 | 300 | | | | |
| 24–2 | 88 | 300 | | | | |
| 27–241 | 77 | 300 | ... | ... | 39 | 300 |
| 27–235 | 94 | 300 | | | | |
| 24–59 | 94 | 300 | ... | ... | 42 | 300 |
| 25–23 | 43 | 300 | | | | |
| 24–25 | 47 | 300 | 19 | 300 | | |
| 27–241 | 69 | 300 | 24 | 300 | 68 | 400 |
| 24–45 | 78 | 300 | | | | |
| 24–26 | 34 | 400 | 15 | 400 | | |
| 24–26 | 47 | 400 | | | | |
| 24–45 | 107 | 600 | | | | |
| 24–59 | 99 | 600 | | | | |
| 24–59 | 95 | 1000 | | | | |
| 25–23 | 84 | 1000 | | | | |
| 24–45 | 112 | 3000 | | | | |
| 24–25 | 62 | 3000 | | | | |

Table 211 gives a summary of the completed experiments dealing with liver fractions and residues. A certain number of experiments with the pernicious anemia liver fraction (Liver Extract No. 343 N.N.R. prepared by Eli Lilly and Company) are included for the sake of completeness. As reported elsewhere[3] this pernicious anemia fraction usually contains about 10 to 20 per cent of the active secondary anemia principle. The residue has not been tested in many experiments but sufficient data are given to show that it contains a liberal amount of the active secondary anemia fraction. Apparently no methods of extraction are available which do not leave behind a good deal of this or other active principle—for example the substance potent in pernicious anemia.

Our main interest centers in the secondary anemia fraction column (Table 211) where a considerable variety of experiments are summarized. For the sake of a *base line* we may say that from the average of a very large number of experiments we expect to find 90 *to* 100 *gm. new hemoglobin* produced by a standard anemic dog as the result of a two-weeks period in which 300 gm. of pig liver are fed daily. Different dogs have individual peculiarities and are geared for greater speed in hemoglobin production and others fall

below the average hemoglobin production. These individual peculiarities are usually quite constant, just as a dog's capacity for running or work may be very different from a litter mate. Dog 24–45 may be cited as a dog whose production is abnormally active on any diet. Dog 24–26 shows an abnormally low output but this is due in part during the past year to a severe pyorrhea.

TABLE 212. — WHOLE LIVER, LIVER FRACTIONS AND RESIDUE IN 300 GRAM EQUIVALENTS DAILY.

Dog 27–241, Coach, Female, Adult.

| Diet periods, 1 week each. Food, gm. per day. | Food cons., per cent. | Weight, kg. | Plasma volume, cc. | R. B. C., millions. | Color index. | Hemoglobin index. | R. B. C. hematocrit, per cent. | Blood hemoglobin level, per cent. | Hemoglobin removed, bled, gm. |
|---|---|---|---|---|---|---|---|---|---|
| Bread, 350; salmon, 100; klim, 25 | 100 | 12.7 | 755 | 3.9 | 0.59 | 2.16 | 21.2 | 46 | 1.4 |
| Liver fraction, secondary anemia* | 100 | 12.6 | 700 | 4.7 | 0.65 | 2.24 | 23.9 | 53 | 30.0 |
| Liver fraction, secondary anemia* | 100 | 12.6 | 728 | 6.5 | 0.51 | 1.96 | 23.9 | 47 | 31.7 |
| Bread, 350; salmon, 100; klim, 25 | 100 | 12.5 | 754 | 6.2 | 0.51 | 2.01 | 19.6 | 39 | 23.5 |
| Bread, 350; salmon, 100; klim, 25 | 100 | 12.5 | 782 | 4.0 | 0.50 | 2.19 | 18.1 | 40 | 1.1 |
| Bread, 350; salmon, 100; klim, 25 | 100 | 12.4 | 748 | 4.5 | 0.50 | 2.13 | 21.1 | 45 | 1.2 |
| Whole pig liver** | 100 | 12.2 | 708 | 7.4 | 0.68 | 2.19 | 28.3 | 62 | 50.2 |
| Whole pig liver** | 100 | 11.9 | 710 | 6.0 | 0.52 | 2.29 | 20.9 | 48 | 28.0 |
| Bread, 350; salmon, 100; klim, 25 | 100 | 12.2 | 726 | 4.9 | 0.52 | 2.13 | 19.7 | 42 | 12.9 |
| Bread, 350; salmon, 100; klim, 25 | 100 | 12.2 | 762 | 4.1 | 0.57 | 2.22 | 21.1 | 47 | 1.5 |
| Liver fraction, secondary anemia† | 100 | 12.5 | 722 | 5.4 | 0.62 | 2.21 | 25.7 | 57 | 33.8 |
| Liver fraction, secondary anemia† | 100 | 12.2 | 763 | 5.1 | 0.55 | 2.27 | 24.3 | 55 | 16.5 |
| Bread, 400; salmon, 75; klim, 25 | 100 | 12.3 | 758 | 5.7 | 0.55 | 2.31 | 20.9 | 48 | 27.4 |
| Bread, 400; salmon, 75; klim, 25 | 100 | 12.7 | 794 | 4.3 | 0.52 | 2.27 | 19.7 | 45 | 1.5 |
| Liver fraction, pernicious anemia‡ | 100 | 12.7 | 766 | 5.7 | 0.48 | 2.08 | 21.8 | 45 | 15.7 |
| Liver fraction, pernicious anemia‡ | 96 | 12.8 | 813 | 4.8 | 0.45 | 2.07 | 20.7 | 43 | 1.4 |
| Bread, 400; salmon, 75; klim, 25 | 99 | 12.8 | 772 | 5.4 | 0.42 | 2.11 | 21.5 | 45 | 1.4 |
| Bread, 400; salmon, 75; klim, 25 | 88 | 13.0 | 826 | 6.0 | 0.43 | 1.84 | 24.1 | 44 | 15.4 |
| Bread, 400; salmon, 75; klim, 25 | 100 | 12.8 | 797 | 4.9 | 0.47 | 1.95 | 23.5 | 46 | 1.3 |
| Liver residue§ | 100 | 13.1 | 819 | 5.6 | 0.46 | 2.21 | 21.5 | 47 | 14.9 |
| Liver residue§ | 100 | 13.4 | 786 | 5.9 | 0.52 | 2.24 | 22.3 | 50 | 28.4 |
| Bread, 400; salmon, 75; klim, 25 | 100 | 13.4 | 752 | 4.8 | 0.44 | 2.08 | 20.3 | 42 | 1.3 |
| Bread, 400; salmon, 75; klim, 25 | 100 | 13.1 | 768 | 5.3 | 0.44 | 2.22 | 21.1 | 47 | 1.4 |

* Bread, 325; salmon, 100; klim, 25.
** Bread, 250.
† Bread, 350; salmon, 100; klim, 25.
‡ Bread, 400; salmon, 75; klim, 25.
§ Bread, 300; salmon, 75; klim, 25.
Standard bread, canned salmon and klim fed daily as indicated.

$$\text{Hemoglobin index} = \frac{\text{Hemoglobin, per cent.}}{\text{Red-cell hematocrit, per cent}}$$

In Table 211 we find that the *average output* of new hemoglobin per two-week period due to this secondary anemia fraction in 300 gm.

liver equivalent daily, amounts to 72 gm. hemoglobin. This is to be compared with the 90 to 100 gm. hemoglobin base line for whole liver. When the intake of this liver fraction is doubled or tripled or increased even ten-fold, we note but little further increase. We have not yet sufficient evidence to establish these hemoglobin output levels for larger intake with the same security as for the 300 gm. equivalent. No clinical disturbance was noted when these large doses of this secondary anemia liver fraction were fed.

Table 212 shows a continuous series of experiments with whole liver and liver fractions in the same standard anemic dog. All conditions are uniform in this experiment and the food intake, body weight and blood-plasma volume remain constant. If we figure the grams hemoglobin produced by this dog per two-week feeding period (see Methods) we record the following amounts: Secondary anemia liver fraction (W 574) produces 77 gm. hemoglobin per two weeks. Whole pig liver produces 87 gm. hemoglobin per two weeks. Secondary anemia liver fraction (W 608-B) produces 69 gm. hemoglobin per two weeks. Pernicious anemia liver fraction (W 608-C) produces 24 gm. hemoglobin per two weeks. Liver residue (W 608-A) produces 39 gm. hemoglobin per two weeks. These last three fractions were made from a single lot of liver as the numerals indicate.

From time to time we notice that there are slight differences in reaction to liver feeding which we are forced to attribute to a varying liver content of this secondary anemia factor. We cannot explain this at present, but suggest that such changes may be observed and later found to be due to the diet intake preceding slaughter of the pigs.

Table 212 shows a significant change in the color and hemoglobin indices when we compare the feeding of whole liver or secondary anemia fractions with the pernicious anemia fraction feeding. The indices are higher in the former and lower during and after the pernicious anemia fraction ingestion. This may indicate that the secondary anemia fraction facilitates more hemoglobin and less stroma production and the reverse for the pernicious anemia fraction.

Table 213 shows the effect of the secondary anemia liver fraction given in the average dose, in double and in ten-fold dosage. We must keep in mind that this dog (24–45) regularly produces more hemoglobin per week than the average dog, no matter what diet is given. This is an individual peculiarity of this dog which is constant year after year which may mean a larger mass of bone marrow or a more efficient liver-marrow machine. We believe there is much evidence that the liver does much of the preliminary construction of hemoglobin factors or a "pigment complex" which is a parent substance of hemoglobin suitable for the finishing touches within the bone marrow.

TABLE 213. — SECONDARY ANEMIA FRACTION IN AVERAGE AND LARGE DOSES.

Dog 24–45, Bull, Female, Adult.

| Diet periods, 1 week each. Food, gm. per day. | Food cons., per cent. | Weight, kg. | Plasma volume, cc. | R. B. C., millions. | Color index. | Hemoglobin index. | R. B. C. hematocrit, per cent. | Blood hemoglobin level, per cent. | Hemoglobin removed, bled, gm. |
|---|---|---|---|---|---|---|---|---|---|
| Bread, 400; salmon, 75 | 100 | 20.4 | 1234 | 4.6 | 0.52 | 2.38 | 20.3 | 48 | 1.4 |
| Liver fraction, 300 equivalent* | 100 | 20.5 | 1136 | 6.1 | 0.57 | 2.50 | 24.5 | 61 | 37.2 |
| Liver fraction, 300 equivalent* | 100 | 20.4 | 1146 | 6.2 | 0.62 | 2.38 | 26.1 | 62 | 26.5 |
| Bread, 400; salmon, 75 | 100 | 20.4 | 1180 | 4.4 | 0.60 | 2.48 | 21.5 | 53 | 15.4 |
| Bread, 400; salmon, 100 | 100 | 21.2 | 1195 | 3.9 | 0.53 | 2.29 | 17.9 | 41 | 1.2 |
| Liver fraction, 600 equivalent† | 100 | 21.3 | 1197 | 4.3 | 0.56 | 2.29 | 21.0 | 48 | 1.5 |
| Liver fraction, 600 equivalent† | 100 | 21.3 | 1106 | 6.5 | 0.55 | 2.36 | 25.9 | 61 | 39.7 |
| Bread, 400; salmon, 100 | 100 | 21.5 | 998 | 5.8 | 0.53 | 2.42 | 24.7 | 60 | 15.1 |
| Bread, 400; salmon, 100 | 100 | 21.5 | 1211 | 5.1 | 0.60 | 2.38 | 23.4 | 56 | 29.2 |
| Bread, 400; salmon, 100 | 100 | 21.6 | 1120 | 4.4 | 0.60 | 2.29 | 20.7 | 47 | 13.8 |
| Bread, 400; salmon, 100 | 100 | 21.3 | 1033 | 3.9 | 0.65 | 2.42 | 19.6 | 47 | 12.3 |
| Bread, 400; salmon, 100 | 100 | 21.4 | 1172 | 4.5 | 0.53 | 2.36 | 20.4 | 48 | 1.6 |
| Bread, 400; salmon, 75 | 100 | 19.9 | 1221 | 4.4 | 0.48 | 2.21 | 19.1 | 42 | 1.2 |
| Liver fraction, 3000 equivalent‡ | 100 | 19.8 | 1128 | 4.8 | 0.54 | 2.21 | 22.5 | 50 | 13.7 |
| Liver fraction, 3000 equivalent‡ | 100 | 20.1 | 1182 | 5.5 | 0.55 | 2.27 | 24.5 | 56 | 31.1 |
| Bread, 400; salmon, 75 | 100 | 20.1 | 1165 | 5.3 | 0.57 | 2.29 | 22.7 | 52 | 35.1 |
| Bread, 400; salmon, 75 | 100 | 20.0 | 1127 | 4.9 | 0.58 | 2.33 | 20.9 | 49 | 27.0 |
| Bread, 400; salmon, 75 | 100 | 19.8 | 1116 | 3.9 | 0.59 | 2.40 | 19.2 | 46 | 1.4 |
| Bread, 400; salmon, 75 | 100 | 19.8 | 1257 | 4.5 | 0.57 | 2.32 | 21.5 | 50 | 14.6 |
| Bread, 400; salmon, 75 | 100 | 19.6 | 1222 | 4.3 | 0.51 | 2.27 | 19.2 | 44 | 1.3 |

* Bread, 400; salmon, 75.
† Bread, 400; salmon, 100.
‡ Bread, 300; salmon, 75.
Standard bread and canned salmon fed daily as indicated.

Double the usual liver fraction intake or 600 gm. equivalent of whole liver daily for two weeks causes a large hemoglobin output or 107 gm. hemoglobin. When ten times the usual amount of this secondary anemia extract is given or 3000 gm. equivalent daily, we observe no increase in the hemoglobin output or 112 gm. hemoglobin per two-week period. Evidently the dog can make effective use of no large surplus of this liver fraction. Other similar experiments are given in Table 211 to show that there may be a moderate increase in hemoglobin production as we increase the intake of the secondary anemia liver fraction from the standard dose of 300 gm. equivalent daily to 600 gm. equivalent. Beyond this point large excess intake will not push up appreciably the hemoglobin output per two-week period.

The 300 gm. equivalent of this secondary anemia liver fraction is not finally established for Dog 24–45 in Table 213 but from average

values and other data on this dog we feel confident that the output will average about 85 gm. hemoglobin per two-week period.

TABLE 214.—VARIOUS LIVER FRACTIONS GIVEN IN 400 GRAM EQUIVALENT DAILY.

Dog 24-26. Bull, Male, Adult.

| Diet periods, 1 week each. Food, gm. per day. | Food cons., per cent. | Weight, kg. | Plasma volume, cc. | R. B. C., millions. | Color index. | Hemoglobin index. | R. B. C. hematocrit, per cent. | Blood hemoglobin level, per cent. | Hemoglobin removed, bled, gm. |
|---|---|---|---|---|---|---|---|---|---|
| Bread, 250; salmon, 100; klim, 25 . . | 100 | 10.5 | 688 | 3.4 | 0.56 | 2.27 | 16.9 | 38 | 1.2 |
| Liver fraction, secondary anemia* . . | 100 | 10.9 | 638 | 4.6 | 0.58 | 2.44 | 25.1 | 61 | 13.6 |
| Liver fraction, secondary anemia* . . | 100 | 10.9 | 661 | 5.0 | 0.55 | 2.42 | 23.4 | 57 | 16.2 |
| Bread, 250; salmon, 100; klim, 25 . . | 100 | 10.7 | 638 | 5.0 | 0.57 | 2.42 | 24.6 | 59 | 13.3 |
| Bread, 250; salmon, 100; klim, 25 . . | 100 | 10.6 | 652 | 4.3 | 0.56 | 2.27 | 21.1 | 48 | 1.5 |
| Liver fraction, secondary anemia, D** . | 100 | 10.6 | 621 | 5.2 | 0.57 | 2.36 | 18.0 | 43 | 22.2 |
| Liver fraction, secondary anemia, D** . | 100 | 10.8 | 672 | 3.8 | 0.51 | 2.24 | 17.4 | 39 | 1.2 |
| Bread, 250; salmon, 75; klim, 25 . . | 100 | 10.5 | 656 | 4.1 | 0.49 | 2.21 | 18.3 | 40 | 1.3 |
| Bread, 250; salmon, 75; klim, 25 . . | 100 | 10.5 | 700 | 4.6 | 0.49 | 2.29 | 19.7 | 45 | 1.4 |
| Liver fraction, secondary anemia, B† . | 95 | 10.5 | 627 | 4.8 | 0.56 | 2.32 | 25.9 | 60 | 12.8 |
| Liver fraction, secondary anemia, B‡ . | 100 | 10.2 | 616 | 5.1 | 0.61 | 2.36 | 17.4 | 41 | 25.8 |
| Bread, 250; salmon, 100; klim, 25 . . | 100 | 10.2 | 644 | 3.2 | 0.72 | 2.34 | 19.8 | 46 | 1.3 |
| Bread, 250; salmon, 100; klim, 25 . . | 100 | 10.4 | 646 | 3.7 | 0.62 | 2.42 | 18.9 | 46 | 1.5 |
| Liver fraction, pernicious anemia, C§ . | 100 | 10.4 | 626 | 4.6 | 0.62 | 2.19 | 17.4 | 38 | 15.9 |
| Liver fraction, pernicious anemia, C§ . | 100 | 10.7 | 687 | 4.0 | 0.41 | 2.22 | 15.0 | 33 | 1.1 |
| Bread, 250; salmon, 100; klim, 25 . . | 72 | 10.2 | 638 | 5.0 | 0.48 | 2.27 | 21.3 | 48 | 1.5 |
| Bread, 250; salmon, 100; klim, 25 . . | 81 | 10.3 | 622 | 4.8 | 0.51 | 2.27 | 21.5 | 49 | 1.5 |

* Bread, 250; salmon, 100; klim, 25.
** Bread, 250; salmon, 100; klim, 25.
† Bread, 225; salmon, 75; klim, 25.
‡ Bread, 175; salmon, 75; klim, 40.
§ Bread, 250; salmon, 100; klim, 25.
Standard bread, canned salmon and klim fed daily as indicated.

Table 214 like Table 212 shows a continuous experimental period on the same dog during which time a number of liver fractions were standardized. This dog during this period was suffering from extensive generalized pyorrhea which undoubtedly is in part responsible for the generally low hemoglobin output figures observed. This dog's standard *base line* for equivalent amounts of whole liver feeding during two-week periods amounts to approximately 60 gm. hemoglobin. With this level we may compare the various fractions as given in Table 214. The first liver fraction (secondary anemia) causes an increased hemoglobin production per two-week period of 47 gm. The next liver fraction, D, is a subfraction and is obtained by methyl alcohol extraction of the secondary anemia fraction. We note only a small increase in blood hemoglobin, which amounts

to but 15 gm. and indicates that a large amount of the potent material is not soluble in methyl alcohol. The third liver fraction, B, is the usual secondary anemia fraction made from the same batch of whole liver as D and C. This fraction (B) is a little less potent than the one used in the first part of this table and shows a hemoglobin increase of 34 gm. above the standard base line of control-bread periods. The last fraction, C, is the usual pernicious anemia fraction corresponding to Liver Extract 343 N.N.R. and it as usual shows but little of the liver potency active in secondary anemia. The hemoglobin output per two-week period is but 15 gm. The intake in all experiments is in 400 gm. equivalents obtained from whole pig liver.

TABLE 215.—SECONDARY ANEMIA FRACTIONS SUPPLEMENTED WITH WHOLE LIVER.

| Diet periods, 1 week each. Food, gm. per day. | Food cons., per cent. | Weight, kg. | Plasma volume, cc. | R. B. C., millions. | Color index. | Hemoglobin index. | R. B. C. hematocrit, per cent. | Blood hemoglobin level, per cent. | Hemoglobin removed, bled, gm. |
|---|---|---|---|---|---|---|---|---|---|
| **Dog 24–2, Bull, Male, Adult.** | | | | | | | | | |
| Bread, 350; salmon, 75; klim, 30 . . | 85 | 15.5 | 997 | 3.4 | 0.59 | 2.22 | 17.8 | 40 | 1.2 |
| Liver fraction, 300 + liver 110* . . . | 100 | 15.5 | 984 | 4.7 | 0.56 | 2.31 | 26.6 | 61 | 15.2 |
| Liver fraction, 300 + liver 110* . . . | 100 | 15.4 | 906 | 6.2 | 0.59 | 2.46 | 21.9 | 54 | 52.0 |
| Bread, 375; salmon, 75; klim, 25 . . | 100 | 15.9 | 990 | 4.2 | 0.61 | 2.46 | 20.8 | 51 | 13.5 |
| Bread, 375; salmon, 75; klim, 25 . . | 71 | 14.8 | 952 | 3.6 | 0.64 | 2.40 | 19.3 | 46 | 1.5 |
| **Dog 25–23, Bull, Male, Adult.** | | | | | | | | | |
| Bread, 350; salmon, 75; klim, 25 . . | 92 | 15.7 | 921 | 2.6 | 0.58 | 2.03 | 14.7 | 30 | 0.8 |
| Liver fraction, 300 + liver 110* . . . | 100 | 14.7 | 814 | 4.0 | 0.80 | 2.27 | 32.6 | 74 | 15.8 |
| Liver fraction, 300 + liver 110* . . . | 100 | 15.5 | 754 | 4.4 | 0.93 | 2.44 | 25.2 | 62 | 50.4 |
| Bread, 375; salmon, 75; klim, 25 . . | 100 | 15.4 | 853 | 3.8 | 0.79 | 2.48 | 18.0 | 45 | 24.6 |
| Bread, 375; salmon, 75; klim, 25 . . | 100 | 15.8 | 900 | 2.9 | 0.90 | 2.40 | 18.9 | 45 | 12.2 |
| Bread, 375; salmon, 75; klim, 25 . . | 100 | 15.5 | 954 | 3.3 | 0.67 | 2.34 | 18.9 | 44 | 1.5 |
| **Dog 24–26, Bull, Male, Adult.** | | | | | | | | | |
| Bread, 275; salmon, 75; klim, 30 . . | 73 | 9.9 | 618 | 3.5 | 0.63 | 2.31 | 19.2 | 44 | 1.2 |
| Liver fraction, 300 + liver 110† . . . | 97 | 10.2 | 597 | 4.6 | 0.61 | 2.46 | 24.3 | 60 | 15.8 |
| Liver fraction, 300 + liver 110‡ . . . | 100 | 10.2 | 606 | 5.2 | 0.66 | 2.50 | 18.4 | 46 | 44.2 |
| Bread, 275; salmon, 75; klim, 25 . . | 100 | 10.2 | 648 | 3.6 | 0.64 | 2.50 | 18.4 | 46 | 1.5 |
| Bread, 275; salmon, 75; klim, 25 . . | 89 | 10.4 | 668 | 4.9 | 0.60 | 2.31 | 18.7 | 43 | 14.4 |
| Bread, 250; salmon, 100; klim, 25 . . | 98 | 10.4 | 694 | 3.0 | 0.55 | 2.27 | 14.6 | 33 | 1.0 |

* Bread, 300; klim, 25.
† Bread, 275; klim, 25.
‡ Bread, 225; klim, 25.

$$\text{Hemoglobin index} = \frac{\text{Hemoglobin, per cent}}{\text{Red-cell hematocrit, per cent}}$$

Table 214 like Table 212 also shows an interesting change in the color and hemoglobin indices. During the feeding periods of the secondary anemia fraction, the color and hemoglobin indices are somewhat higher than normal and during and after the feeding of the pernicious anemia fraction we observe somewhat lower figures for the color and hemoglobin indices. This may indicate that the secondary anemia liver fraction is somewhat more favorable for hemoglobin production and the pernicious anemia fraction more favorable for red-cell stroma production.

Table 215 shows the result of supplementing the secondary anemia fraction with small amounts of whole pig liver. The liver fraction is given in 300 gm. equivalent + 110 gm. whole fresh liver equivalent. The mixture is fed daily for the two-week period. The results are somewhat irregular and are not conclusive. The first experiment Dog 24–2, Table 215, shows an output of 80 gm. hemoglobin per two-week period of liver extract and whole-liver feeding. This same dog on secondary anemia liver fraction of 300 gm. equivalent (see Table 211) shows an output of 88 gm. under similar conditions. This would indicate no supplementary effect of the whole liver.

The next experiment—Dog 25–23, Table 215—shows a very different result and the combined liver fraction plus whole liver gives a high output of new hemoglobin of 108 gm. per two weeks. This same dog (Table 211) shows a low output on the secondary anemia liver fraction alone amounting to but 43 gm. hemoglobin per two weeks. This would indicate a very significant supplementary effect due to the whole liver.

The last experiment—Dog 24–26, Table 215—shows a similar result to the preceding. The combined liver fraction plus whole liver gives an output of 58 gm. hemoglobin per two weeks which is distinctly above the low output observed in this dog during the feeding of the secondary anemia fraction alone—40± gm. hemoglobin per two-week period. This conflicting evidence leaves us in some uncertainty about the value of a small supplementary feeding of whole liver added to the dosage of the secondary anemia fraction. These observations are not unlike those obtained in earlier experiments[3] with a pernicious anemia fraction (Liver Extract 343 N.N.R.). We suggested that whole liver in small doses might add to the potency of the liver fraction (343) as measured by the new formed hemoglobin in secondary anemia in dogs.

We have evidence that supplementing the secondary anemia *liver* extract with small amounts of whole kidney will likewise show a supplementary effect. We hope to report soon a series of experiments with a secondary anemia fraction obtained from kidney tissue.

Table 216 gives some evidence that iron and this secondary anemia fraction of liver may supplement each other and give hemoglobin

production values above the average figures for the liver fraction alone. Dog 24–2, Table 216, shows a large hemoglobin output as a result of a two-week daily optimum intake of ferric citrate (Fe 40 mg.) and the secondary anemia liver fraction (300 gm. equivalent) This figures out as 91 gm. hemoglobin production. We may compare this with an experiment (Table 211) on the same dog where the liver fraction alone gave a hemoglobin output of 88 gm. per two-week period. Obviously there is no evidence here for a favorable reaction to the iron intake but the evidence is positive in the last two experiments.

TABLE 216.—SECONDARY ANEMIA LIVER FRACTION + IRON.

| Diet periods, 1 week each. Food, gm. per day. | Food cons., per cent. | Weight, kg. | Plasma volume, cc. | R. B. C., millions. | Color index. | Hemoglobin index. | R. B. C. hematocrit, per cent. | Blood hemoglobin level, per cent. | Hemoglobin removed, bled, gm. |
|---|---|---|---|---|---|---|---|---|---|
| **Dog 24–2, Bull, Male, Adult.** | | | | | | | | | |
| Bread, 350; salmon, 75; klim, 25 . . | 100 | 16.1 | 973 | 4.1 | 0.52 | 2.24 | 19.2 | 43 | **1.1** |
| Liver fraction + iron* . . . . . | 100 | 15.6 | 864 | 5.6 | 0.54 | 2.29 | 32.6 | 75 | **33.7** |
| Liver fraction + iron* . . . . . | 100 | 15.6 | 878 | 5.7 | 0.62 | 2.40 | 20.6 | 49 | **53.4** |
| Bread, 375; salmon, 75; klim, 25 . . | 100 | 15.4 | 853 | 5.0 | 0.52 | 2.40 | 17.6 | 42 | **14.3** |
| Bread, 375; salmon, 75; klim, 25 . . | 100 | 15.6 | 945 | 3.9 | 0.55 | 2.36 | 18.5 | 43 | **1.3** |
| Bread, 350; salmon, 75; klim, 30 . . | 85 | 15.5 | 997 | 3.4 | 0.59 | 2.22 | 17.8 | 40 | **1.2** |
| **Dog 27–241, Coach, Female, Adult.** | | | | | | | | | |
| Bread, 400; salmon, 75; klim, 25 . . | 100 | 13.1 | 768 | 5.3 | 0.44 | 2.22 | 21.1 | 47 | **1.4** |
| Liver fraction + iron† . . . . . | 100 | 13.3 | 710 | 6.7 | 0.52 | 2.26 | 29.9 | 67 | **41.3** |
| Liver fraction + iron† . . . . . | 100 | 13.4 | 705 | 6.2 | 0.59 | 2.46 | 26.3 | 65 | **47.1** |
| Bread, 400; salmon, 75; klim, 25 . . | 100 | 13.5 | 730 | 5.1 | 0.57 | 2.40 | 20.0 | 48 | **28.8** |
| Bread, 400; salmon, 75; klim, 25 . . | 100 | 13.5 | 727 | 4.3 | 0.53 | 2.27 | 20.4 | 46 | **1.3** |
| **Dog 24–26, Bull, Male, Adult.** | | | | | | | | | |
| Bread, 275; salmon, 100; klim, 30 . . | 100 | 10.1 | 638 | 3.6 | 0.64 | 2.46 | 18.7 | 46 | **1.3** |
| Liver fraction + iron‡ . . . . . | 100 | 10.3 | 612 | 4.7 | 0.64 | 2.34 | 21.5 | 50 | **23.7** |
| Liver fraction + iron‡ . . . . . | 100 | 10.4 | 631 | 4.6 | 0.63 | 2.42 | 22.2 | 54 | **28.1** |
| Bread, 275; salmon, 75; klim, 30 . . | 98 | 10.4 | 647 | 3.9 | 0.67 | 2.50 | 20.5 | 51 | **12.6** |
| Bread, 275; salmon, 75; klim, 30 . . | 97 | 10.3 | 615 | 4.2 | 0.62 | 2.34 | 16.5 | 39 | **11.6** |
| Bread, 275; salmon, 75; klim, 30 . . | 73 | 9.9 | 618 | 3.5 | 0.63 | 2.31 | 19.2 | 44 | **1.2** |

* Liver fraction, 300 grams equivalent; bread, 350; salmon, 75; klim, 25; given daily.
† Liver fraction, 300 grams equivalent; bread, 400; salmon, 75; klim, 25; given daily.
‡ Liver fraction, 400 grams equivalent; bread, 275; salmon, 100; klim, 25; given daily.
Iron, 40 mg., daily given in food as ferric citrate.

Dog 27–241, Table 216, gives convincing evidence that the iron salt and the liver fraction do supplement each other. This dog on the liver fraction alone (Table 211) shows a hemoglobin output of

69 to 77 gm. per two-week period. When we supplement this intake of the secondary anemia liver fraction (300 gm. equivalent daily) with ferric citrate (40 mg. Fe daily) we observe a high total hemoglobin output of 110 gm. per two-week feeding.

Dog 24–26, Table 216, also gives similar evidence that an iron salt and this liver fraction supplement each other. This dog (Table 211) on an intake of the secondary anemia liver fraction (400 gm. equivalent daily) shows a hemoglobin output of about 40 gm. hemoglobin. When the same dose of this liver fraction is fed plus ferric citrate (40 mg. Fe daily) we note a definite rise in hemoglobin output amounting to 65 gm. hemoglobin per two-week feeding.

TABLE 217.—SECONDARY ANEMIA LIVER FRACTION—ASHED.

| Diet periods, 1 week each. Food, gm. per day. | Food cons., per cent. | Weight, kg. | Plasma volume, cc. | R. B. C., millions. | Color index. | Hemoglobin index. | R. B. C. hematocrit, per cent. | Blood hemoglobin level, per cent. | Hemoglobin removed, bled, gm. |
|---|---|---|---|---|---|---|---|---|---|
| **Dog 27–241, Coach, Female, Adult.** | | | | | | | | | |
| Bread, 400; salmon, 75; kilm, 25 | 100 | 13.5 | 727 | 4.3 | 0.53 | 2.27 | 20.4 | 46 | 1.3 |
| Liver fraction, ashed* | 100 | 13.6 | 722 | 5.4 | 0.59 | 2.24 | 25.0 | 56 | 35.2 |
| Liver fraction, ashed* | 100 | 14.1 | 752 | 4.8 | 0.55 | 2.38 | 23.1 | 55 | 18.1 |
| Bread, 400; salmon, 75; klim, 25 | 100 | 14.1 | 845 | 5.8 | 0.57 | 2.19 | 17.1 | 37 | 29.2 |
| Bread, 400; salmon, 75; klim, 25 | 100 | 14.4 | 820 | 4.1 | 0.51 | 2.26 | 18.7 | 42 | 1.2 |
| **Dog 24–45, Bull, Female, Adult.** | | | | | | | | | |
| Bread, 400; salmon, 75 | 100 | 19.6 | 1222 | 4.3 | 0.51 | 2.27 | 19.2 | 44 | 1.3 |
| Liver fraction, ashed† | 100 | 19.8 | 1216 | 3.9 | 0.55 | 2.31 | 18.7 | 43 | 1.3 |
| Liver fraction, ashed† | 100 | 19.8 | 1116 | 5.4 | 0.59 | 2.31 | 25.0 | 58 | 37.4 |
| Bread, 400; salmon, 75 | 100 | 20.0 | 1160 | 4.9 | 0.52 | 2.31 | 22.8 | 53 | 13.9 |
| Bread, 400; salmon, 75 | 100 | 19.9 | 1151 | 4.7 | 0.56 | 2.42 | 20.5 | 50 | 15.0 |
| Bread, 400; salmon, 75 | 100 | 20.2 | 1189 | 4.7 | 0.51 | 2.46 | 17.9 | 44 | 11.8 |
| Bread, 400; salmon, 75 | 100 | 20.4 | 1234 | 4.6 | 0.52 | 2.38 | 20.3 | 48 | 1.4 |
| **Dog 24–25, Bull, Male, Adult.** | | | | | | | | | |
| Bread, 350; salmon, 75; klim, 25 | 100 | 14.3 | 923 | 3.1 | 0.76 | 2.50 | 18.8 | 47 | 1.3 |
| Liver fraction, ashed‡ | 100 | 14.8 | 868 | 3.5 | 0.66 | 2.42 | 19.2 | 46 | 1.4 |
| Liver fraction, ashed‡ | 100 | 14.0 | 862 | 5.5 | 0.64 | 2.29 | 19.1 | 44 | 36.1 |
| Bread, 400; salmon, 75; klim, 25 | 100 | 14.2 | 870 | 4.5 | 0.62 | 2.34 | 17.9 | 42 | 13.7 |
| Bread, 400; salmon, 75; klim, 25 | 97 | 13.9 | 927 | 3.6 | 0.61 | .42 | 8.0 | 44 | 1.3 |

Liver fraction ash given in 300 gm. equivalent daily.
* Bread, 400; salmon, 75; klim, 25; daily diet.
† Bread, 400; salmon, 75; daily diet.
‡ Bread, 350; salmon, 75; klim, 25; daily diet.

Table 217 gives interesting information about the *ash* of this secondary anemia fraction. We may recall that an optimum iron

salt intake may show an average hemoglobin output per two-week feeding of 50 gm. These ash experiments show average values of 60 gm. hemoglobin produced per two-week feeding, when the ash from 300 gm. equivalent of this secondary anemia fraction is given. The optimum iron intake[10] is 40 mg. daily and this ash as fed contains 10 mg. iron as metal per 300 gm. equivalent, so that other salts would seem to be concerned.

This ash gives very similar results when compared with the ash from whole liver[1] although the ashing methods are somewhat different. The ash obtained from whole liver was subjected to a more destructive process which may have burned off some salts not destroyed by the muffle method used on this secondary anemia liver fraction which was ashed. This may explain why the ash of this liver fraction runs a little higher than whole-liver ash as measured by hemoglobin production in anemic dogs.

**Discussion.** Does liver therapy benefit human cases of secondary anemia? This is not the place to review the considerable mass of clinical papers which are accumulating rapidly because of a developing inquiry in this field. Reports for and against liver therapy are numerous. We believe in many of the negative reports that the liver feeding was inadequate in amount and duration. Possibly the reason for this may be outlined somewhat as follows: Liver therapy in pernicious anemia is spectacular and results are obvious within two weeks, with large production of new red cells and a rapid rise in blood hemoglobin. By contrast the reaction in secondary anemia is less striking and may be delayed. There are facts which explain these differences and it may be worth reviewing them briefly at this time.

*Pernicious anemia* is a disease in which there is a great surplus of hemoglobin pigment and related pigments. The red cells are saturated with the maximum content of hemoglobin. The muscle hemoglobin is high in spite of anemia and inactivity, which tend to lower the muscle hemoglobin level. The blood serum and body fluids contain an excess of pigments related to the blood hemoglobin. The urine and feces contain an excess of pigment which is related to blood hemoglobin. On the basis of the pathologic findings in the blood, bone marrow and organs, Whipple[5,6] several years ago proposed an explanation for these findings in pernicious anemia, *not* on the basis of red-cell *destruction*, but on the basis of faulty *construction* or the lack of red-cell stroma constituents. This explanation fits in with the observed facts to date and gives a ready explanation for the spectacular regeneration of red cells in pernicious anemia following liver feeding. We may assume that the liver feeding supplies the missing element necessary for maturation of the red-cell stroma, that large reserves of pigment building materials as well as pigment are stored in the body and the red cells are then produced in extraordinary members.

*Secondary anemia* in direct contrast to pernicious anemia is a disease in which there is a *deficit* of hemoglobin pigment and related pigments. The red cells are lacking in normal content of hemoglobin and consequently there is a relative excess of stroma. The body pigments are subnormal in concentration and there are no excess pigment derivatives unless active red-cell destruction is in progress. Evidently the normal blood-forming organs under the stimulus of a low blood-hemoglobin level can produce stroma more actively than new hemoglobin. The reserves of parent hemoglobin material or building stones suitable for new hemoglobin fabrication are exhausted or reduced and can be restored only through food intake—organic and inorganic. We have experimental evidence to be published soon that infection and intoxication can delay the new hemoglobin production in normal hyperplastic bone marrow in dogs.

All these facts suggest why the reaction to liver therapy is bound to be less spectacular in secondary anemia than in pernicious anemia but do not lessen the importance of liver therapy in secondary anemia. It has been proved beyond a reasonable doubt that liver and kidney in the diet furnish the maximum supply of substances most suitable for new red-cell and hemoglobin fabrication. It is not always easy for an anemic patient to take the required amount of liver or kidney. This secondary anemia liver fraction described above may be of service in certain cases of this type.

*Iron* must be mentioned in any discussion of secondary anemia but need not be reviewed in detail as this has been done very recently.[10] It may be stated that the optimum intake of iron from salts and food has been established for the dog in experimental anemia as about 60 mg. iron as metal daily. Above this level of intake a large excess of iron salts gives no further rise in the production of hemoglobin. It appears to make no difference whether iron is given as ferrous chlorid, ferric citrate, ferrous carbonate, ferrous sulphate or ferrous ammonium sulphate. The optimum total intake of iron exceeds three-fold the loss of iron by bleeding and wastage of red cells. It is obvious that this iron has some effect in the body other than that of mere replacement of iron in the lost or worn-out hemoglobin. This iron in excess of hemoglobin iron requirements obviously exerts some influence upon internal body metabolism so that more hemoglobin is produced. We may call this a salt effect and it is probably similar to the effect noted with feeding salt mixtures, copper and other metals, and ash from liver and kidney.

**Summary.** A liver fraction is described which contains 65 to 75 per cent the potency of whole liver for new hemoglobin production in experimental anemia due to hemorrhage. This fraction represents 3 per cent of the weight of the whole liver.

Probably a number of active substances are represented in this liver fraction. Inorganic substances are important.

Supplementing this liver fraction with iron may increase the total output of hemoglobin. The same thing is true for whole liver feeding plus iron which may give maximal hemoglobin production in experimental anemia.

Supplementing this liver fraction with small amounts of whole liver may increase the total output of new hemoglobin above the level due to liver fraction alone.

These experimental observations will be of greater interest when compared with similar controlled observations in various human secondary anemias.

This liver fraction is palatable and can be taken in considerable amounts without clinical disturbance.

Reasons are given why liver therapy is so spectacular in pernicious anemia and notably less effective in certain secondary anemias.

We urge that liver therapy should not be considered inert in any type of secondary anemia until it has been given a thorough test.

All evidence available points to liver and kidney as supplying the essential factors in most available form for the reconstruction of new hemoglobin and red cells in anemia.

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## RHINAL MYIASIS.

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Rhinal myiasis, nasal myiasis, or myiasis narium, the infestation of the nasal cavity with fly larvæ, is said to be of fairly common occurrence in certain countries of Asia and Africa, as well as in tropical and subtropical portions of America. In North India, where the condition is reported to be especially frequent, it is known

as "peenash," and many cases are far advanced before medical aid is sought. According to one writer, screw-worm myiasis is common in the Americas from the Argentine to Canada, but Blain questions this assertion in so far as it applies to the states of Pennsylvania and Michigan. Stitt observes that the screw-worm fly is common over nearly all of North and South America. Cases of human nasal myiasis have been reported from Arizona, Iowa, Kansas, southern California, New Mexico, Texas and probably from other states in this country, but the literature on the subject is by no means voluminous. Blain, referring to myiasis in general, states that "the disease is probably far more common in man than is generally supposed." Yount and Sudler collected reports of 23 cases occurring in Arizona in the course of one season. Sporadic instances are apt to occur wherever the screw-worm fly is prevalent; however, in the United States the incidence of the nasal form of the disease is not sufficiently large to deprive the occasional case of interest, and for that reason 2 case reports are presented with this article.

**Etiology.** In the New World, human myiasis is produced by several different species of flies. The common screw-worm fly, Chrysomyia macellaria, is the usual offender in this region. This is a dipterous insect of the suborder Cyclorrhapha. It is distinguished from the ordinary blue-bottle fly by the presence of three longitudinal black stripes arranged symmetrically on the thorax or scutum. It is a small fly about 1 cm. to ½ inch in length. The head is short, of a red or yellow color and is closely attached to the body, which latter is covered with stiff black hairs and presents a bluish or greenish metallic appearance. The female lays from 200 to 300 eggs or more. These eggs hatch in a few hours when deposited in a favorable environment. The larvæ are described as "whitish, footless grubs, rather slender and quite active." They reach maturity in five to six days, at which time they are from ½ to ¾ inch long. They have twelve segments with a belt of minute spines or bristles around each segment. They are largest near the posterior end, tapering almost to a point at the head, thus somewhat resembling a screw, from which is derived their name. On reaching maturity they drop to the ground and there, burying themselves, pass through the pupal stage to develop into the adult fly. The pupæ are brown, elongated oval in shape and about 1 cm. long. The pupa stage occupies from nine to twelve days, but varies somewhat and may be as long as fourteen days. Thus, the metamorphoses involved in the development from egg to adult fly extend over a period of two to three weeks, so that a number of generations may be bred in a single season. In rhinal myiasis the larvæ occur in the nose as facultative parasites, and from there invade the surrounding tissues, the paranasal sinuses or even penetrate the bone. Other diptera of the same family may cause the disease, notably Calliphora vomitoria and Lucilia cæsar; sometimes also members

of the related family Sarcophagidæ may be responsible for the condition. In short, a number of different genera of flies have been indicted as the causative agents of myiasis narium.

The exciting cause of the disease is, of course, the larvæ themselves, but aside from this, several predisposing or contributory factors may be mentioned in considering the etiology. The most important of these seems to be the presence of preëxisting pathologic conditions of the nose. In both cases here reported there was an antecedent chronic nasal disease; in 1 case of undetermined, but probably luetic, character; in the other, an atrophic rhinitis. Such factors have been present in other reported cases. Dixon's case had had a slight epistaxis the day preceding that on which the fly entered his nose. McColloch reports 2 cases from Laredo, Texas, in both of which there was chronic atrophic rhinitis. Ozena seems to present an especially inviting field for ovipositing to some species of flies, and it is thought that the offensive odor attracts them, likewise after epistaxis the smell of blood guides the fly to the unfortunate victim. Yount believes that chronic rhinitis or even uncleanliness predisposes to the disease. Among predisposing affections noted are also chronic nasal catarrh, epithelioma and luetic rhinitis; the presence of the disease itself invites reinfection.

Sleeping in the open affords the fly an opportunity to deposit its eggs undisturbed, and hence is of great importance as a contributory cause. McColloch's 2 cases and my first case were infected in this way. Yount and Sudler also describe 2 cases similarly infected, 1 in a morphin habitué, the other in an alcoholic during a drunken debauch.

The climate and season of the year, inasmuch as they affect the habits of the flies which cause the disease, also affect its prevalence. The seasonal incidence varies with the latitude, as the flies are not active during cold weather, hence in the northern hemisphere cases are apt to occur earlier in the year as we approach the equator. We should also expect to find a larger number of cases in the warmer climates, where the flies have longer periods of activity and are more numerous, and, judging from available data, this is the true state of affairs. The disease occurs in both sexes, but is more frequent in the male, whose habits of life expose him more often to the infection. For the same reason, the disease is commoner in the country than in the cities, and is seen more often in the poor than among the well-to-do. It occurs most often in farmers and others whose occupation consists of open-air work in the rural districts.

In studying an active case there is usually obtainable a history of a fly in the nose two or three days before the onset of symptoms. When the patient is not seen until the disease is well developed, he may be in such a condition as to preclude the possibility of securing any history at all unless the relatives or friends can supply the missing data. In one case the dead fly was blown from the nostril

several days after the onset of symptoms, and since the patient was asleep when the fly entered, he had no knowledge of its presence. The eggs in the favorable environment in which they are deposited hatch out in twenty-four hours or less, but the movements of the larvæ may not be perceived by the patient. The young parasites migrate farther up into the nasal cavity, feeding on the discharge present from antecedent causes or due to the irritation caused by their presence. Patton maintains that the larvæ can imbibe only fluids, but that their toxic salivary secretion in conjunction with the inevitable secondary bacterial infection breaks down the tissues of the host, although the worms themselves cannot feed directly on the tissues. He further states that they are unable to make their way through bone, and hence cannot enter the brain; but this contention is at variance with the statements of other writers. In Snow's case the hyoid bone was destroyed, and the palate bone so greatly damaged that it broke on the slightest pressure. In 1 of the Arizona cases, reported by Dr. Looney, "destruction of the soft and bony tissue was such that one could look from the lower border of the frontal bone directly into the esophagus through an opening 2½ inches wide by 3½ inches long."

**Symptomatology.** Subjective symptoms are noted in from one to three days from the time the eggs are deposited in the nose, and in both cases here described partial obstruction to breathing on the affected side was the first evidence of the disease noticed by the patient. Sometimes there is first noticed a feeling of discomfort or a peculiar sensation at the root of the nose, radiating outward along the supraorbital ridge. This gradually increases, until it becomes an intense pain, most frequently located over the frontal sinuses, but may perhaps be felt in the maxillary region, the temporal region, or occasionally in the region of the ear. In one instance severe headache persisted for a week after all the larvæ had been removed. Early subjective symptoms are accompanied or soon followed by a serosanguinous nasal discharge which is characterized by a foul odor. The discharge becomes more profuse and appears also, but in smaller amount, from the other nostril as the disease advances. It then assumes a more purulent aspect, being thicker and of a dirty reddish-brown color, while the odor is so offensive as to be nauseating. Dixon observes that the presence of blood in the discharge indicates the activity of live worms in the tissues. After destruction or removal of the larvæ, as the patient begins to improve, the blood disappears from the discharge, which then becomes mucopurulent or mucoseropurulent and rapidly diminishes in quantity, to disappear finally as convalescence is established.

Coincident with the beginning of the nasal discharge, the patient begins to clear his throat and expectorates frequently or develops a loose cough which brings up a purulent material. Sometimes sneezing is an early symptom. After treatment is instituted, or

even before, the sputum is apt to contain a few living or dead larvæ which have made their way or have been washed by irrigating fluids into the nasopharynx. There is intense irritation in the nose. Pyrexia sets in, the temperature rising to 101° or 102° F. Headache and neuralgia are usually marked, especially on invasion of the sinuses by the parasites. The nose, eyelids and cheeks swell, the swelling arising first and being more pronounced on the affected side, but also involving the opposite side. The irritative eye signs of lachrymation redness, photophobia and blepharospasm develop, the bulbar and palpebral conjunctivæ are irritated or inflamed and mucopurulent material gathers at the inner canthi. Subjective sensation of activity within the nasal chambers has developed by this time and the swarming larvæ can be seen in active motion. The number of larvæ varies from a score or more up to several hundred. As the disease advances, the surface over the swelling becomes discolored, resembling erysipelas in appearance, and the destruction of tissue may even extend to the surface of the face, breaking down the skin to produce a foul open sore. In some cases movement of the larvæ has been discernible under the intact skin. The nasal conchæ may be destroyed, the septum and palate perforated and the parasites not infrequently make their way into the paranasal sinuses, occasionally into the orbit, even entering the bulbus oculi, or, according to some writers, may even invade the intracranial space and the brain, in which event secondary bacterial invasion results in a fatal issue.

The condition of the psyche in the early stages is marked by anxiety and depression. However, as the disease progresses and toxic symptoms develop, apathy supervenes which gradually, in spite of mental irritation at ineffective attempts to clear the nose, deepens into stupor or even into coma. In a case reported by Franchini and in the second case reported here the psyche remained undulled, but there was extreme nervous irritability and restlessness. In some cases there is delirium or a semidelirious state. With the improvement of the condition in the nose, the mental symptoms clear up with remarkable promptness.

Some observers include pallor and loss of weight among the objective symptoms of the disease. Epistaxis may appear in the active stage or may be a late symptom. Barlara reports a case from Argentina, in which the patient succumbed to hemorrhage after apparently having been cured. The hemorrhage in my second case was a delayed symptom, but fortunately did not result fatally.

**Diagnosis.** The diagnosis is made by observing the larvæ. Early in the disease they may be perceived more easily after shrinking the swollen mucous membrane with cocain and adrenalin, later they are seen without difficulty high in the nasal cavity and still later may make their appearance in the nasal fossæ, be expectorated from the nasopharynx or appear at artificial openings of their own forma-

tion. Before the larvæ are seen, however, their presence may be suspected. Especially in the warmer climates, a patient developing nasal obstruction, foul nasal sanguinopurulent discharge and intense irritation in the nose should be suspected of having nasal myiasis; a history of a fly in the nose several days before makes the diagnosis almost certain. Few conditions are apt to be confused with that under discussion. When the first symptoms appear the presence of an intranasal foreign body might be hypothecated by the observer, or perhaps local inflammatory swelling from some other cause might be considered as a possible diagnosis. However, even at this stage of the disease, the larvæ may be made out if the nasal cavity is carefully inspected with a good light. If they are still unseen, chloroform may be successful in bringing them to view.

After the disease is fully developed it may present the appearance of erysipelas, anthrax, acute paranasal sinusitis, cellulitis of the face or noma; but there should be no difficulty in making the correct diagnosis at this time as the larvæ are readily observed.

**Complications.** Complications in the main are due to extension of the destructive process into adjacent structures, together with the migration of the larvæ into the surrounding tissues or sinuses. Perhaps the commonest of all complications is paranasal sinusitis, and of the sinuses the frontal seems to be the one most frequently involved. Otitis media with suppuration was reported in one of the Arizona cases. Migration of the larvæ into the orbit or into the cranial cavity has already been mentioned. Hemorrhage may occur in serious or even fatal proportions. Gastric and intestinal myiasis may rarely be complications or sequelæ. Inspiration pneumonia is occasionally met with. General sepsis and septic meningitis are said to be encountered, but seem to be rare, as infrequent mention of them is made in the literature.

**Prognosis.** The seriousness of the disease is indicated by the report of Yount and Sudler of a series of 23 cases of myiasis, with a mortality of 22 per cent in 18 nasal cases. The prognosis is governed largely by the severity of the symptoms and time of beginning treatment. Where but a few larvæ are present the outlook is more favorable. Preëxisting diseases, such as chronic nephritis or organic heart trouble may determine a fatal issue. As the larvæ mature in a few days the period of disability is relatively short, unless prolonged by complications, reinfections or sequelæ. Death may occur from exhaustion, hemorrhage, sepsis, meningitis or pneumonia. If the patient escapes a fatal termination, varying degrees of deformity may result from tissue destruction—saddle nose, perforated septum, perforated palate or destruction of portions of the nose or cheek may occur. Patterson recorded a case which resulted in complete destruction of the nose and part of the face. The conchæ and nasal septum are commonly attacked. When ozena was present before hand, it is apt to be made worse when portions of the mucous

membranes lining the nasal cavities are destroyed. If larvæ enter the eyeball, loss of the eye may result. Franchini reports a case where spontaneous recovery took place, but was followed by intestinal myiasis.

**Treatment.** Treatment may be divided into preventive or prophylactic and active. Of great importance in the prevention of the disease is the treatment and where possible the cure of any intranasal pathology. In cases of ozena or other conditions which may not be entirely eradicable, or which tend to recur, the patient should be warned of the danger of myiasis. He should also be cautioned against sleeping in the open unscreened. Where exposure is considered likely the anterior nares may be plugged with cotton wool soaked in antiseptic. Finally, in event a fly enters the nose, the patient should report to a doctor at once for removal of the eggs, in the event any should have been deposited. Approaching the problem from another angle, prevention of breeding of the flies whose larvæ cause the condition may to a great degree be brought about by the proper disposal of refuse and of the carcasses of dead animals.

The active treatment is further divided into curative and symptomatic. The curative treatment consists in the removal of the larvæ and the use of measures to promote healing of the lesions they have caused. Removal of the larvæ is accomplished in part mechanically and in part by the use of drugs. McColloch reports mechanical extraction of the larvæ at successive sittings at two- or three-hour intervals after chloroform had proved ineffective. Other writers advise the removal of as many larvæ as possible mechanically at one sitting, followed by the use of drugs. A number of drugs have been recommended for this purpose. Jeanselme and Rist advise the injection of pure benzene into the nasal cavities. Turpentine, ether, phenol solution and chloroform are also of value. Stevens states that irrigation with 5 per cent phenol is the best treatment. Chloroform, however, appears to be the more widely used, and is employed in several different manners. The vapor may be inhaled, or as in Dixon's case, pledgets of cotton saturated with undiluted chloroform may be inserted into each nostril. The pledgets were kept saturated and were left in place five minutes. Blain advised chloroform in the strength of from 25 per cent to the pure drug. Stiles advises washing with 20 per cent chloroform in milk or with phenol solution. Patton advises the use of weak chloroform water or the local application of turpentine, and states that the larvæ should not be killed *in situ* as they are then a source of secondary infection. Yount and Sudler obtained their best results by spraying chloroform, 25 per cent to the pure drug, from a syringe with a spray tip "ejecting the chloroform with considerable force up into the nasal chambers and, if possible, their accessory sinuses." Olive oil is used as the diluent. Immediately after spraying the nose

larvæ are searched for and removed with forceps. This procedure is carried out twice a day until all larvæ have been removed. The plan of treatment generally chosen seems to be the use of chloroform in one of the methods described, combined with removal of accessible larvæ with forceps immediately thereafter, this sequence being repeated at intervals varying in length of time with different workers. As an adjuvant line of therapy various bland irrigations have been recommended to promote cleanliness or to allay the stench accompanying the disease. Normal salt solution, boric acid solution, 1 to 4000, potassium permanganate solution or chloroform water may be used as often as indicated.

The symptomatic treatment meets the indications as they arise, and general hygienic measures are enforced. Pain usually requires the use of morphin, but may be amenable to coal-tar preparations or codein. Nervousness, anxiety and insomnia may yield to bromids or other hypnotics. In weakened states stimulative and supportive measures are called for. If the patient's mind is clear the repulsive nature of his malady robs him of any desire of eating, but liquid and semiliquid foods may be well taken. Finally, plastic surgery may be indicated for the correction of deformities resultant from the disease.

**Case Reports.** CASE I.—J. S., colored, aged seventeen years, of Raywood, Texas, a well-developed, fairly well-nourished French negro of low-grade mentality. When first seen on night of September 25, he lay in the dorsal decubitus in a stuporous condition. The eyelids of the left eye were edematous and the eye was closed by the swelling. The conjunctivæ of both eyes were red and injected and at inner canthus of each a bead of mucopurulent material had gathered. Lachrymation and photophobia were well-developed symptoms. The nose and adjacent portion of the face on each side were also swollen and edematous. The nasal cavities were occluded and breathing was through the mouth, which remained constantly open except when the patient swallowed or expectorated. A foul-smelling sanguinopurulent fluid of dirty reddish-brown color trickled slowly from the nose. Two old perforations of the palate were present and a history of some form of nasal trouble having existed over a long period of time suggested the first diagnostic consideration of chronic syphilitic rhinitis with secondary septic infection. The temperature was 101.4° F. Two days prior to this the nasal cavities had become obstructed, but at that time there was no discharge, and since then the patient's condition had been growing progressively worse. No active movement could be observed inside the nasal cavity, and as far as could be determined, there was no subjective sensation of active movements. Antiluetic treatment was instituted and, in addition, continuous wet dressings to the face and solution of mild silver salt instilled in the eyes and nose at regular intervals.

The following morning the temperature had dropped to 99.6° F., and the patient's general condition appeared slightly improved, although the swelling and edema showed no perceptible change. On September 27, active motion was detected in the nose and the true condition realized. Ether having been successfully employed in treating dermal myiasis, this drug was used for nasal irrigation in 50 per cent solution in olive oil. A few larvæ came out dead with the irrigating fluid, others were removed with tissue forceps afterward, some dead and some alive. Some were embedded

in the tissues and were pulled out with some difficulty. Even the dead ones presented a rasplike resistance to removal due to the spines on the segments. Forty larvæ were removed at this time.

On September 28, edema had increased some, extending further to the left than to the right. The left nostril was distended, being packed tightly with larvæ, evenly arranged and presenting somewhat of a honeycomb appearance in the aggregate. A few larvæ were discerned on the right side. The septum was perforated. Any attempt to remove larvæ with forceps would initiate a rapid scramble of the parasites further up into the nasal cavity. A small fresh perforation of the soft palate was present through which a larva could occasionally be seen. The nose was irrigated with chloroform in milk, the fluid being carried to the upper parts of the cavity by means of a soft rubber catheter. About 25 more larvæ were removed. The same afternoon no living larvæ could be seen. Some dead ones had passed. Some had been swallowed, causing vomiting, but none were observed in the feces and no gastrointestinal symptoms developed. No accurate count of the number had been kept. The patient complained of intense headache over right frontal sinus. Codein and aspirin were given for this with amelioration but without complete relief.

On September 29, considerable swelling of the soft palate with redness and difficult deglutition. Discharge from nose scanty. Edema reduced. Patient brighter and becoming talkative. He stated that on September 26 he blew a dead fly out of his nose, but did not know how long it had been in there. Several days before that he did not remember exactly how many, he had lain down under a tree in the yard for a nap, and probably the fly entered while he was asleep.

Recovery was uneventful, but no follow-up of the case could be made as the patient migrated to Louisiana as soon as he was able to travel.

The larvæ were the typical screw worms and were classified as Chrysomyia macellaria larvæ.

Case II.—M. J., white, aged twelve years, of Liberty County, Texas. On October 7, date of first visit, the patient was in bed, very restless, changing position at frequent intervals and, although not complaining of any pain, was evidently experiencing much discomfort. The temperature was 100.8° F. There was a partial obstruction to breathing in the right nostril and from the right anterior naris a drop of brownish serous discharge would emerge at frequent intervals. The patient was making frequent attempts to dislodge the obstruction in his right nostril, stopping left nostril by pressing side of nose with finger and blowing vigorously through the right. Nothing emerged, however, except the discharge previously referred to. There was a slight discharge from the left nostril which was rimmed with dried secretion. There was a collection of purulent material in corner of the right eye, and considerable swelling, most pronounced on right side beside the nose. The loose tissues under the right eye were slightly puffed. There was an offensive musty odor to discharge. The psyche was clear.

On October 1, the boy had been riding through the woods on a truck and a fly flew in his nose. It was there for only a moment, as the patient at once began efforts at dislodgement which were readily effective. On October 4, he blew some hard object from his nose and that evening began to have a little fever. On October 5, the nose began to discharge a serosanguinous fluid, and the face began to swell on right side next to nose.

On October 8, temperature was 101° F. The swelling had increased. The right eye was almost closed; the nasal discharge was brighter red and more profuse. On examination, larvæ could be seen moving about high up in the right side of the nose for the first time seven days after the dead fly had been blown out. The nose was irrigated with 20 per cent chloroform

in milk; only four worms were removed. The same fluid was dropped in with a medicine dropper every thirty minutes.

On October 9, temperature was 100° F.; pulse, 76. No worms after 10 A.M. Total worms removed, 169, all but a few of which were dead when expelled. Profuse bright serosanguinous discharge.

On October 10, the patient was up; had no fever. Moderate amount of mucoseropurulent discharge from right nostril. Patient discharged from treatment with directions for after care.

On October 11, a hurry call to see the patient again, who had blown a piece of necrotic tissue about 1 by 2 cm. from nose; copious hemorrhage from left nostril followed. This continued for about one hour, stopping shortly before my arrival. A short while after this the patient blew another larva from the nose. This was said to be somewhat larger than the others and proved to be the last. Total number of larvæ, 170.

On November 15, the nose had healed. Septum deflected to left in lower portion; no perforation seen. Right inferior turbinate almost completely destroyed, a small beadlike projection on outer nasal wall being the only visible remnant. Ozena persists as before intercurrent affliction. The larvæ in this case did not present typical screw-worm appearance, being smoother, rounder and somewhat smaller. Unfortunately, they were not identified.

**Summary.** 1. While fairly common in some parts of the world, rhinal myiasis is not of frequent occurrence in the United States, though perhaps more so than the number of reported cases would indicate. Two cases are reported herewith.

2. Several different genera of flies have been found to cause the disease. The screw-worm fly, Chrysomyia macellaria, is, however, most often the causative agent in this region.

3. Antecedent nasal disease is important as a predisposing factor in the development of the condition. Sleeping in the open, unscreened, favors the infestation. Other etiologic influences are dependent on the habits and prevalence of the flies and the frequency of human exposure.

4. The cardinal symptoms are nasal obstruction with foul nasal sanguinopurulent discharge and intense irritation in the nose. Pain is usually present and often severe. Swelling is more marked on the affected side, but involves both sides as the disease progresses. There is moderate elevation of the temperature. Hemorrhage is not unusual and may be a delayed symptom. Tissue destruction is sometimes extensive. Mental symptoms vary from anxiety and restlessness to stupor or coma.

5. The diagnosis is made by observing the larvæ in the nose.

6. Paranasal sinusitis is the most frequent complication. Other complications arise from migration of the larvæ into other structures and from accompanying bacterial infections. Epistaxis may occur in fatal proportions. Inspiration pneumonia may develop or rarely general sepsis or septic meningitis.

7. The prognosis may be guarded due to the high mortality and the frequency of complications. Prognostic criteria which may indicate a more or a less favorable outcome are the general physical condition of the patient, the magnitude of the infection, the stage

of the disease at the time of beginning treatment and the presence or absence of complications.

8. Though a number of different drugs have been advocated in the treatment of rhinal myiasis, the therapeutic procedure generally adopted in this country is the use of chloroform by one of several methods, combined with the mechanical removal of accessible larvæ. Symptomatic treatment meets the indications as they arise.

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# ANEMIA IN JAUNDICE.*

## I. A Clinical Study of Cases in Which Jaundice Was of Obstructive or Intrahepatic Types.*

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Anemia is commonly seen in patients with jaundice that is due to obstruction of the common duct by stone, stricture, carcinoma of the head of the pancreas, or malignant disease of the biliary passages and in patients with jaundice due to intrahepatic causes. The anemia may be moderate or relatively severe and it may occur independently of fever, chills, hemorrhage or other clinical evidences of infection or of loss of blood.

In an effort to throw some light on the etiology of the anemia which occurs in jaundiced patients, a preliminary survey was made of those cases of jaundice observed at the Clinic during the last two and a half years. This survey was undertaken in order to determine the frequency with which anemia occurred in each of the various types of jaundice, the degree of the anemia and the relationship, if any, between the intensity of the anemia and either the duration or the intensity of the jaundice. Our chief interest was in those patients who presented anemia without any clinical evidence of infection or loss of blood. Consequently those with chills, fever, leukocytosis, purpura, melena, hematemesis or hematuria were not included in the present group of cases used for drawing conclusions regarding the relationships of jaundice and anemia. An attempt has also been made to study this type of anemia experimentally in animals, and the results of this work will be reported elsewhere. A group of 347 cases of jaundice was made the basis of the study reviewed here.

Anemia was considered to be present if the value of hemoglobin was below 70 per cent (Dare) and if the erythrocyte count was below 4,000,000 per c.mm. Of this group of 347 cases, 329 were observed during the years 1926 and 1927, and in 90 of the latter anemia was

* The data presented in this paper are taken from a thesis submitted by F. M. Jordan to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of M.S. in Medicine, 1929.

present. To this number, 18 selected cases with anemia, observed in 1925, were added, making a total of 108 cases of anemia. In determining the frequency with which anemia occurred, the group of 329 cases observed during 1926 and 1927 was selected, but for the remainder of the data the entire group of 347 cases was selected. The diagnosis was confirmed in most cases by operation or by necropsy. In some cases, including nearly all of those of intrahepatic jaundice, the diagnosis depended on the clinical data, the behavior of the patients while under observation and the subsequent course after they left the hospital.

**Carcinoma.** In the majority of the patients who had carcinoma the lesion was in the head of the pancreas. The few remaining patients in this group had carcinoma of the gall bladder or biliary ducts, and one or two had biliary obstruction as a result of metastasis of carcinoma of the stomach or colon to the regional lymph nodes. Of the total number of 347 cases of jaundice, there was carcinoma in 81, in 33 of which anemia was present (tabulation). Anemia occurred in 25 of 73 cases observed during 1926 and 1927 (34 per cent). The lowest percentage of hemoglobin was 38, with an average of 56. The lowest erythrocyte count was 2,650,000, with an average of 3,470,000. By comparing the amount of serum bilirubin, the erythrocyte count, the percentage of hemoglobin and the duration of jaundice, curves were constructed to show the correlation between the intensity of the anemia and either the duration or the intensity of jaundice. So far as this group of patients was concerned, there did not appear to be any correlation clinically between the intensity of the anemia and either the duration or intensity of the jaundice (Figs. 1 and 2).

OCCURRENCE OF ANEMIA IN PATIENTS WHO HAD JAUNDICE.

| Group. | Total cases. | Total cases of anemia. | Cases in 1926–1927. | Cases of anemia in 1926–1927. | Per cent of cases of anemia in 1926–1927. | Average hemoglobin, per cent. | Average erythrocytes (millions). |
|---|---|---|---|---|---|---|---|
| Carcinoma | 81 | 33 | 73 | 25 | 34.2 | 55.7 | 3.47 |
| Intrahepatic jaundice | 93 | 31 | 90 | 28 | 31.1 | 59.0 | 3.61 |
| Cholelithiasis | 142 | 30 | 138 | 26 | 19.2 | 61.0 | 3.67 |
| Stricture | 31 | 14 | 28 | 11 | 39.3 | 59.0 | 3.62 |
| Totals | 347 | 108 | 329 | 90 | | | |

**Intrahepatic Jaundice.** All cases of arsphenamin jaundice, catarrhal jaundice and biliary cirrhosis were included under the common heading of intrahepatic jaundice, according to McNee's classification. Of the total number of 347 cases of jaundice, 93 belonged to this group, in 31 of which anemia was present (tabulation). Anemia

occurred in 28 of 90 cases (31 per cent) observed in 1926 and 1927. The lowest erythrocyte count was 2,700,000 and the average count was 3,610,000. The lowest percentage of hemoglobin was 40, with an average of 59. As in the preceding group, there did not appear to be any definite correlation clinically between either the intensity or duration of the jaundice and the anemia occurring in this group of cases (Figs. 1 and 2).

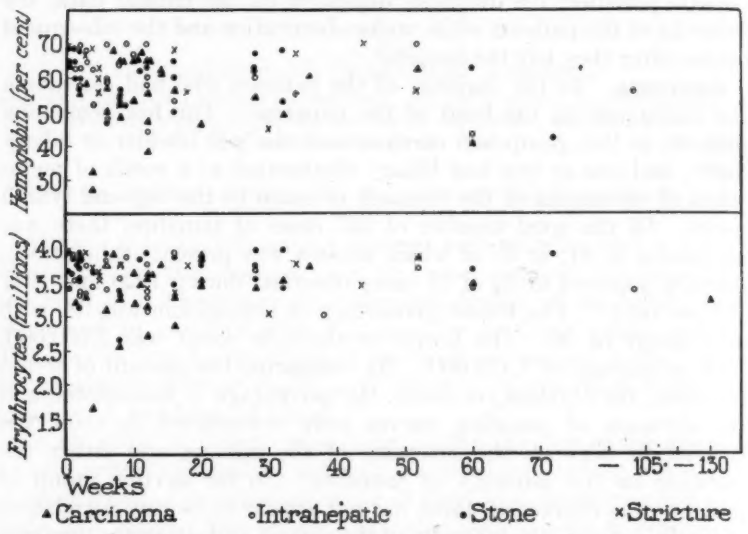


FIG. 1.—Correlation between the duration of jaundice and the degree of anemia in cases with a percentage of hemoglobin between 70 (Dare) and an erythrocyte count below 4,000,000 per c.mm.

**Cholelithiasis.** In this group are included all cases of jaundice due to stone in the common duct or to cholecystitis with cholelithiasis. Fever occurs in the majority of cases during an acute attack of colic due to cholelithiasis. Since the attack is of short duration fever was usually absent when these patients came to the Clinic; therefore, jaundice was the chief presenting symptom. Consequently, included in this group are patients with jaundice of several days' or weeks' duration who did not have fever between acute attacks of colic. Of the total number of 347 cases of jaundice, 142 belonged to this group, in 30 of which anemia was present (tabulation). Anemia occurred in 26 of 138 cases (19 per cent) observed in 1926 and 1927. The lowest percentage of hemoglobin was 42, with an average of 61. The lowest erythrocyte count was 3,400,000 and the average count was 3,670,000. Again a definite correlation could not be seen between the intensity of the anemia and either the duration or the intensity of jaundice (Figs. 1 and 2).

**Stricture of the Common Duct.** Since fever is present at some time in the majority of the cases of jaundice that is due to stricture of

the common duct, it is difficult to be certain that, when anemia was present in the cases of this group, infection may not have been a contributing factor. Thirty-one cases of stricture of the common duct were found, however, in which there was no history of fever and in which neither fever nor leukocytosis was present during the period of observation; in 14 of these 31 cases anemia was present (tabulation). Anemia occurred in 11 of 28 cases (39.3 per cent) observed in 1926 and 1927. The lowest percentage of hemoglobin was 45, with an average of 59. The lowest erythrocyte count was 3,010,000, with an average of 3,620,000. There was no definite correlation between the intensity of the anemia and either the intensity or the duration of the jaundice (Figs. 1 and 2).

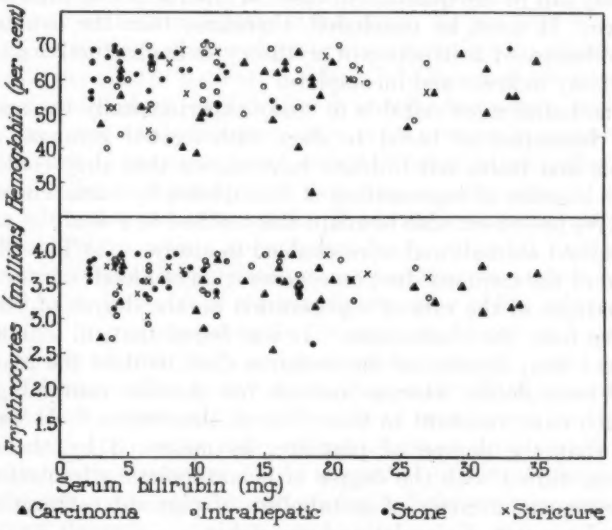


FIG. 2.—Correlation between the degree of jaundice and the degree of anemia in cases with a percentage of hemoglobin below 70 (Dare) and an erythrocyte count below 4,000,000 per c.mm.

**Comment.** The anemia that occurs in cases of obstructive and intrahepatic jaundice may be due to loss of blood, to increased destruction of blood, to decreased formation of blood or to a combination of these various factors.

It is well known that bile salts are hemolytic and the suggestion is commonly made that the anemia is due to the hemolytic action of these salts. There are many objections to this view. It is known that following a preliminary rise in the concentration of bile salts in the blood after obstruction of the common duct in dogs and human beings there is a gradual falling off in the level of these salts in the blood. We should expect, therefore, if bile salts were the cause of the anemia, to obtain anemia very soon after the onset of jaundice, when the concentration of bile salts is greatest. As

we have seen, this is by no means the case. In clinical cases, at least, the onset of the anemia is variable and may occur early or late. In dogs the anemia increases coincidently with a fall in the concentration of bile salts in the blood.[5] A point of great significance is that the concentration of bile salts necessary to produce hemolysis, as determined *in vitro*, does not occur in clinical or experimental cases of jaundice. Moreover, it must be remembered that there is increased resistance of the erythrocytes, and a protective action of normal serum against hemolytic agents.[1,3,4] It is difficult to obtain direct experimental evidence on the question of hemolysis. The question is usually studied by determining the amount of bile excreted in dogs with biliary fistulas, but this is obviously out of the question in cases of obstructive or intrahepatic jaundice. It must be concluded, therefore, that the evidence in favor of increased destruction of erythrocytes in obstructive jaundice is relatively indirect and incomplete.

It was found more suitable to study experimentally the question of the formation of blood in dogs with ligated common ducts. Whipple and Robscheit-Robbins have shown that they could control the amount of regeneration of hemoglobin by variations in the diet. We have been able to adapt this method to a study of anemia in jaundiced animals and were enabled to study: (1) The effect of ligation of the common duct on regeneration of blood; (2) the effect of variations in the rate of regeneration on the degree of jaundice resulting from the obstruction. It was found that, in animals fed the basal diet, ligation of the common duct inhibits the regeneration of hemoglobin, whereas animals fed the diet containing liver are much more resistant to this effect of obstruction.[2] It was also found that the degree of jaundice, as measured by the serum bilirubin, varied with the degree of hematopoietic stimulation and the consequent activity of metabolism of pigment rather than on the total amount of circulating hemoglobin.

From the clinical standpoint, it is difficult to obtain quantitative data because of the many uncontrollable factors involved, such as the degree of obstruction or of hepatic injury, the degree and duration of jaundice and the character of the diet prior to admission of the patient to the hospital. The experimental results seem to show the importance of certain food factors in the prevention of anemia.

Experimentally, we have also shown that the degree of hematopoietic stimulation influences the degree of jaundice. If anemia develops in a jaundiced patient because of nutritional disturbance, we should, therefore, expect the degree of jaundice to diminish in intensity. Consequently, if anemia occurs in a jaundiced patient, independently of infection or of loss of blood, the amount of serum bilirubin diminishes so that the degree of jaundice alone does not give an accurate index of his condition. Under such circumstances, an anemic patient with low serum bilirubin may be a poorer risk

than one with a higher value of serum bilirubin in the absence of anemia.

**Summary and Conclusions.** Anemia frequently occurs in jaundice due to any cause, and it may be independent of infection or of loss of blood. Similar anemia occurs in dogs with obstruction of the common duct or with biliary fistula. In this series of patients there did not appear to be any correlation between the degree of anemia and either the duration or the intensity of jaundice, whether the jaundice was due to carcinoma, stone, stricture or intrahepatic disease. Anemia, represented by a value of hemoglobin below 70 per cent on the Dare scale, and below 4,000,000 erythrocytes occurred in 34 per cent of patients with jaundice due to carcinoma of the pancreas or biliary passages or to metastasis; in 31 per cent of patients with intrahepatic jaundice; in 19 per cent of patients with stone in the common duct or cholecystitis with cholelithiasis, and in 39 per cent of patients in whom jaundice was due to stricture of the common duct. Clinically, it is difficult to draw conclusions as to the cause of the anemia, since there are many uncontrollable factors, such as the reaction of each particular patient, the amount of obstruction or injury to the liver and the character of the diet before admission to the hospital. However, comparison is possible with animals in which anemia has been produced and studied. When this is done the conclusion is reached that the anemia is almost certainly not the result of the hemolytic action of bile salts and that nutritional factors are probably the most significant in its etiology.

Moderate or relatively severe secondary anemia may occur in cases of jaundice due to any cause, independently of infection or of loss of blood. Clinically, in this series of cases the intensity of the anemia was apparently independent of either the intensity or the duration of the jaundice. It is suggested that nutritional factors are of great significance in the etiology of the anemia occurring in jaundiced patients.

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# NEPHROSIS.

## A Survey of the Literature, and Report of Four Cases.

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There are a number of affections of the kidney which are characterized by degenerative changes especially involving the tubules. These seem to be distinct from the inflammatory conditions which involve the glomeruli, and are also quite different from the arteriosclerotic diseases of the kidney. These affections have gradually acquired the name of "nephrosis." This term is not used in its etymologic sense, but, regardless of frequent objection, has retained such a widespread use that for the present, at least, we might as well accept it. The name was introduced first by Müller,[1] in 1905, and was intended to distinguish the degenerative from the inflammatory changes in the kidney. In 1914, in their monograph on Bright's disease, Volhard and Fahr[2] adopted this term as descriptive of degenerative affections of the kidney involving the tubules.

There are several different types of nephrosis. For instance, the kidney of pregnancy is generally placed in this class on account of albuminoid degeneration found in the convoluted tubules. This type is characterized clinically by albuminuria, edema, and possibly eclampsia during pregnancy. Amyloid nephrosis is another form. It occurs in the course of tuberculosis, expecially of the bones, and is found in prolonged suppurative conditions such as osteomyelitis of nontuberculous origin. Here it is mainly characterized by albuminuria, and when edema is present it is generally combined with lipoid nephrosis. The kidney condition seen in mercuric poisoning also comes under the heading of nephrosis and presents a good example of the necrotic stage of this disease.

This disease, in which only tubular changes occur, is supposed to run a definite clinical course; without renal insufficiency, without hypertension, and without cardiac hypertrophy. Everyone understands, however, that kidney disease seldom pursues a clear-cut course and that one type of nephritis often merges into another. This may occur, obviously, in many variations and various degrees, and accounts for the many confusing differences we meet with in the study of kidney cases. One may say in general, that inflammatory processes affect the glomeruli, and the tubules become involved secondarily; while the degenerative processes affect primarily the tubules and the glomeruli secondarily. It is important to realize that confusion must always exist in diagnosing this disease, since in most cases one type of lesion becomes engrafted on the other.

For this same reason, nephrosis in its pure state is comparatively rare. Munk[3] classifies the nephroses under the following types: (1) Albuminous degeneration; (2) fatty degeneration; (3) lipoid degeneration; (4) necrotic degeneration; (5) hyaline degeneration; (6) amyloid degeneration; (7) vacuolar degeneration; (8) glycogen degeneration (in diabetes).

We find, then, several different conditions giving rise to degeneration of the tubules, or what we have come to term nephrosis, for instance: (1) The kidney of pregnancy; (2) the amyloid kidney; (3) the bichlorid kidney. These are probably separated because of differences in etiology, and because there are some slight clinical distinctions; the common factor to all, however, is the tubular lesion.

That pure types of nephrosis occur, seems no longer a matter of dispute, and among the different types of this disease the one to receive the most discussion nowadays is the so-called "lipoid nephrosis." This is the same disease, characterized by the large white kidney, which used to be called chronic parenchymatous nephritis. It is what Volhard and Fahr[2] refer to as "genuine nephrosis" and what Epstein[4] calls "chronic nephrosis." Pure cases of this disease have been reported by Volhard and Fahr[2] and later by Munk[5] in their monographs, and it is to these authors that we owe most of our knowledge of this disease from abroad. In this country the interest in this condition has centered around Epstein[6] following his introduction of high-protein feeding. Since then many cases of nephrosis have appeared in the literature. A good many of them seem to be cases of glomerulitis to which nephrosis has become an added factor and a good many seem to be cases of genuine nephrosis.

Lipoid nephrosis as an entity has definite characteristics which we find described by Munk.[5] These features are: The insidious onset; its relative frequency in young people; the absence of etiologic factors; the pallor; the edema, which is generally cyclic in character; the albuminuria with few casts and no red blood cells; a low blood pressure; and an increase in the blood cholesterol. He also points out the apparently benign character of the disease. The urine is scanty as a rule, there may be lassitude, headaches and loss of appetite. Munk was the first to call attention to the doubly refracting lipoid bodies in the urine. To these factors Epstein[6] adds: reduction in the total protein of the blood, stresses the "inversion of the normal ratio of serum albumen to serum globulin," and brings out the argument that nephrosis is of extrarenal origin, and apparently a metabolic disease accompanied by a lowered basal metabolism. Epstein[7] records a case of nephrosis which finally developed into one of genuine myxedema. He also mentions three cases of nephrosis which developed during prolonged irradiation of the neck, involving the chest and thyroid.

The lowered basal metabolism certainly suggests that this is a metabolic disease. It appears so on the surface at least, until one is confronted with the fact that these basal metabolic readings are based on water-logged conditions. These individuals are edematous and this must affect the test considerably. The disturbance, however, is apparently not measurable in basal metabolic determinations since only 60 per cent of Epstein's cases show subnormal findings and these ranging only from −10 to −22. On the other hand, he finds that these patients tolerate enormous doses of thyroid extract; doses of 15 to 60 grains of thyroid per day being necessary in some cases. This treatment must often be continued over long periods of time before a metabolic response is elicited. He finds that thyrotoxic symptoms do not result as long as there is an existing hypercholesterolemia, and suggests that the blood cholesterol be used as a measure of thyroid therapy in these cases. This seems to point to some profound metabolic disorder, and since it appears to be extrarenal, he has chosen the name "diabetes albuminuricus" to describe the disorder. In his opinion the extrarenal factors are of prime importance; the tubular degeneration is a consequence, and not a cause of the disease. Hence, he prefers that the term "nephrosis" shall take in all kidney conditions where the dominant lesion is tubular degeneration; but since lipoid nephrosis is not in a strict sense a kidney disease, he prefers the term diabetes albuminuricus. In diabetes the glycosuria is the result of a perversion in carbohydrate metabolism, so in this disease, the albuminuria which is the chief symptom, is the result of a perversion of the protein metabolism.

Munk's cases of lipoid nephrosis and Epstein's cases of chronic nephrosis seem to be identical and appear to be a definite disease entity despite the refusal of some authors to recognize it. It seems to me that we have cases enough now reported by reliable authors to convince the most skeptical. Beside Volhard and Fahr's, Munk's and Epstein's cases, there are numerous others listed in the literature, many of which appear to be true nephrosis and some of which seem to be mixed in type. Some authors complain that they are unable to find cases of a pure form and on account of this are inclined to disbelieve in its existence. The pure cases of nephrosis, however, are rare; the majority which we see are cases of glomerular nephritis with a superimposed nephrosis. These are generally the cases in which we find red blood cells in the urine. Munk's original conception was that the condition in the tubules is at no time the result of inflammation, and this I believe is the general opinion now. There are still some differences of opinion, however; Elwyn[8] believes the albuminuria is the result of injury to the glomerular and capsular epithelium by a previous acute diffuse nephritis which has subsided. Murphy and Warfield report 4 cases. One of these cases was studied from beginning to end, and on examining the kidneys they found no evidence of any glomerular inflammatory condition; the

disease was purely tubular. Another point these authors bring out is the tendency to exacerbations and remissions; that is, the cyclic character of the edema which they claim is the rule. Mason[10] reports a case of what seems to be pure nephrosis which he followed for thirty months, and which finally died of miliary tuberculosis. The kidneys showed a typical contracted nephrotic kidney without signs of inflammation. Kaufman and Mason[11] reported 3 cases (deaths from infection) which they believe typify the life history of nephrosis. Their first case showed all the clinical requirements of an early nephrosis, and at autopsy showed a large white kidney; the glomeruli were normal, but the tubules were dilated and filled with a pale-staining structureless material. Some of the tubular epithelium had desquamated, while the rest was granular and hazy in outline. There was no inflammatory exudate, and no increase of fibrous connective tissue. The second case, in addition to the characteristics of Case I, showed a moderate rise in blood pressure and some impairment in the nitrogen excretion. The kidneys were contracted. The third case showed in the early part of his illness all the characteristics of Case I and in the terminal part showed the characteristics of Case II. At autopsy, this case showed secondary contracted kidneys. They believe that the true nephrotic kidney progresses into a secondary contracted one, as a result of an organizing process of degenerated cells, and not of cells primarily inflamed. Davidson[12] reports a case with autopsy with typical clinical findings. Microscopic examination showed that the glomeruli were singularly free from damage and that the typical tubular changes were present. Peters[13] reports 6 cases, but only 1 of these seems to me to be a case of true nephrosis. Major and Helwig[14] report a case fulfilling the clinical requirements, but the glomeruli showed a mild glomerulitis. Rabinowitch and Childs[15] cite a case, but their patient had hypertension, and was probably a chronic nephritic with a superimposed nephrosis. Rigler and Rypins[16] report 3 cases which conform clinically to Epstein's nephrosis; one was a child, and a postmortem examination showed the large white kidney. McElroy[17] reports 2 cases in negroes; the first case was preceded by tonsillitis, and by the presence of occasional red blood cells in the urine. This might be considered a mixture of acute nephritis and nephrosis. The pathology of the kidney, however, in this case was that of nephrosis so that occasional red blood cells in the urine are permissible just as they may be found present quite normally in health. There was no sign of inflammation in the kidneys. The second case was complicated by syphilis. Munk[5] gives syphilis as a cause of this disease. Cases of nephrosis in children occur frequently. Twenty-three of these have been reported by Clausen,[18] 26 by Davison and Salinger,[19] and 13 by Boyd.[20] Christian[21] states that in some twenty odd years of interest in the subject, he has seen no such cases. All his cases, apparently having all the criteria as outlined, have shown

quite marked glomerular lesions. There is not much doubt in the minds of those who have studied this subject, however, that nephrosis does occur and occurs as a pure tubular degeneration with definite and characteristic findings.

**Diagnosis.** The characteristics then of nephrosis are: (1) A gradual onset and a protracted course; (2) edema, anasarca, and effusion in the serous cavities; (3) oliguria, and a high specific gravity; (4) marked albuminuria and occasional cylindruria; (5) the absence of increased blood pressure; (6) the absence of nitrogen retention in the blood; (7) marked increase in the cholesterol content of the blood; (8) reduction in the total protein of the blood serum; (9) inversion of the normal ratio of albumin to globulin; (10) the presence of doubly refracting lipoid bodies in the urine; (11) it tends to occur more commonly in younger individuals; (12) there seems to be some relationship to states of hypothyroidism.

The edema and albuminuria are the most marked features. These features have been pointed out by Murphy and Warfield[9] as particularly cyclic in character. Epstein[6] explains the edema on the basis of a disturbance in the balance of the osmotic pressure between the tissues and the blood.

It is rather interesting that these patients as a rule show a lowered resistance to disease. Most of the deaths occur from pneumonia, empyema or peritonitis.

**Pathology.** The kidneys in these individuals are large and later become contracted. The capsule strips easily. There are no hemorrhages to be made out, and no signs of inflammation. McElroy[17] finds the cortex widened. The normal markings are obscured and opaque spots corresponding to the deposition of lipoids may sometimes be seen. Microscopically the glomeruli may show focal degenerative changes characterized by widening, and swelling of the capillary walls and of the parietal layer of the capsule; double refracting substances are seen in old cases, and here and there is seen slight nuclear increase. The proximal convoluted tubules are chiefly involved, showing fatty degeneration of the epithelium, or lipoid infiltration. Sometimes there is desquamation of the degenerated cells, exudation of albumin into the lumen, widening of the tubules with flattening of the epithelium, casts and efforts towards regeneration.

**Etiology.** The etiology of nephrosis is obscure, but several theories have been offered. The general impression prevails that it is a disease of extrarenal origin. In 1916, De Renzende[22] reported spontaneous cure of a case following influenzal pneumonia. He also quotes a case reported by Allbutt very similar to his. He seems to think that the cure was due to some foreign protein reaction. Marriott,[23] in 1924, reported the recovery of a case following treatment of the nasal sinuses. Clausen[18] believes the disease to be due to a toxic substance, and finds it associated

with staphylococcus infection principally of the nasal sinuses, and believes it to be a general disorder due to focal infection. In 11 cases, he finds nasal sinus infection invariably present. Aldrich[24] reports 7 cases; all had definite nasal sinus infection and successful drainage gave constant and prompt relief. Many attacks of nephrosis subsided with the spontaneous improvement of nasal sinus infections. Tonsillectomy was done in all his cases but no beneficial effects on the nephrosis were noted. Epstein's[25] theory that it is a metabolic disease and entirely extrarenal is a popular one, especially in the face of the results obtained by thyroid feeding and high-protein diet. Elwyn[8] feels that although nephrosis occurs alone, a glomerular nephritis is so commonly mixed with it that glomerulitis must not be overlooked as a cause. He believes a great many cases begin as an acute glomerulitis.

**Treatment.** The principal treatment of nephrosis consists in the removal of foci of infection with special attention to the nasal sinuses and with restoration of the lost body protein by high-protein diet. Also fluid restriction and salt restriction is advised. Epstein[25] has advocated feeding large quantities of thyroid extract and using the blood cholesterol as a control (enough extract must be used to effect a reduction in cholesterol.) He also takes care of the edema by replacing the lost blood protein by feeding a diet high in protein, free of fat and carbohydrate poor.

**Prognosis.** Regarding the prognosis, several authors report cures by the removal of foci of infection followed by high-protein feeding. Epstein[25] states "certain cases of chronic nephrosis are susceptible to complete cure by the intelligent and persistent use high-protein feeding and thyroid therapy." Intercurrent infections carry off most of these patients.

**Case Reports.** CASE I.—(16236R) female, single, born and lives in Pennsylvania. Employed as a stenographer and is aged forty-eight years.

On admission, April 24, 1925, patient complained of swollen legs and ankles, and had been told by her doctor that she had acute Bright's disease. She did not notice anything particularly wrong until January, 1925, when she first noticed that her urine was becoming very frothy. She went to her physician who informed her that there was a good deal of albumin in the urine. Her face and ankles became swollen, so that she was put on a diet at home. The urine was very scanty. She has suffered no pain or discomfort. There has been no dyspnea, in fact, excepting for feeling a trifle tired, the patient feels well. The only abnormal findings on physical examination were badly swollen feet and legs. The heart appeared to be normal. The urine contained granular and hyaline casts. There were no red blood cells. There was 0.2 per cent or more of albumin present in all specimens. It looked like an extremely bad nephritic urine, but on examining her blood we found her blood chemistry to be normal, or even below normal. Urea nitrogen was 9.45 mg. per 100 cc.; uric acid 3.6, and creatinin 1.2. The phthalein test showed a kidney function of 78 per cent for the two hours and when checked up later showed 51 per cent. The ratio between the day and night volume was normal. The specific gravity varied from 1.007 to 1.018, the patient, however, was drinking large quantities of water

at this time. From the clinical appearance and judging from the urine analysis, therefore, this case might easily be pronounced a severe nephritic, yet her other kidney studies and blood chemistry findings argues against nephritis. It occurred to us that we were dealing with a case of chronic nephrosis. In keeping with this diagnosis we next found that the plasma cholesterol was increased to 0.406 per cent. The basal metabolism was −20. The patient was somewhat anemic. The relation between the serum albumin and globulin was only done once, but was found to be normal. Her blood pressure was 120 systolic and 76 diastolic.

The patient was put on a high-protein diet, 150 gm., and thyroid extract 0.5 grain t.i.d. At the end of four days the edema had almost disappeared. The high-protein diet was then discontinued for fear of injury to the kidneys and the dose of thyroid extract was doubled. The swelling immediately reappeared and by the end of four days was again as bad as ever. It was then decided advisable to try the diuretic effect of calcium chlorid, 12 gm. per day, on the patient. The result was an immediate diuresis and decrease in the edema, so that the patient lost 6¼ pounds in weight in the following three days. The patient was discharged and ordered to continue this treatment. A letter from her one month later, reported that she was feeling "just fine" and the edema had not returned.

On returning home this patient continued to use thyroid extract, 0.5 grain t.i.d. and calcium chlorid, 4 gm. t.i.d. She wrote me on October 24 complaining of indigestion and urticaria in the form of hives. We then changed her medicine to calcium lactate and parathyroid, 0.05 grain t.i.d. She immediately improved and in a letter from her dated April 25, 1929, she states that she has never had any swelling of any kind since. She feels well in every way and apparently has nothing at all the matter with her.

**Case Summary.** This case seems to have been one of genuine nephrosis. The disease has entirely cleared up and after four years has shown no sign of return. Treatment consisted of the extraction of abscessed teeth, high-protein diet, thyroid extract, large doses of calcium chlorid, and finally giving her parathyroid and calcium lactate. Just which of these therapeutic measures resulted in the cure is difficult to say. The high-protein diet appeared to be the principal factor at first, but on discontinuing this, the calcium chlorid seemed to have the same effect. In any event, this patient finally recovered after the high-protein diet had been discontinued. The thyroid extract was given with all the other medications, so that it would seem that this and the calcium chlorid was the principal factor.

Case II.—(26950R) female, married, aged forty-one years. Employed as a practical nurse.

The patient was admitted in November, 1928, complaining of kidney trouble. Her history was to the effect that six weeks prior to admission her legs began to bloat for the first time. They improved a little and then she had a relapse. The edema increased so that she was suspected of having nephritis and the urine consequently examined by her home physician. It was found to boil solid, and on consultation with one of the members of our staff, nephrosis was suggested. The patient was then brought here for study. There were no symptoms of any kind except the swelling of the legs. She had never had any previous kidney upset and had had her urine examined twice a year for some time, always finding it normal. In the past the only diseases from whch she suffered were measles, whooping cough and chicken pox. She had had one child, who is aged twenty-one years. The family history was negative.

Physical examination on admission showed very marked edema of the legs with some general anasarca. She weighed 215 pounds. Her blood pressure was 108 systolic and 90 diastolic. The tonsils were diseased. The

teeth had been entirely removed. The remainder of her examination was negative.

Laboratory reports showed that the urine coagulated solid. There were no red blood cells present. Specimens contained some finely granular and coarsely granular and hyaline casts. The phthalein test showed a kidney function of 37 per cent for the two hours. Blood count on November 15 showed erythrocytes, 5,500,000; leukocytes, 10,000; hemoglobin, 93 per cent; the differential count was normal. The specific gravity of the urine varied from 1.011 to 1.030 but on nearly all occasions showed a high specific gravity. Culture of the urine was negative. The blood Wassermann was negative. Blood chemistry studies on November 15, 1928, showed blood sugar, 0.075 per cent; urea nitrogen, 10.9; uric acid, 5.2; creatinin, 1.4; calcium, 9.3 mg. per 100 cc.; cholesterol, 0.44 per cent. A basal metabolism on November 17 was −21. On November 19, the nonprotein nitrogen (serum) was 18.4 and total nonprotein nitrogen (plasma) 16.7 mg. per 100 cc.; total protein serum, 3.37 per cent; total protein plasma, 3.66 per cent; serum albumin, 1.89 per cent; plasma albumin, 1.66 per cent; serum globulin, 1.48 per cent; plasma globulin, 2 per cent. On December 12, urea nitrogen 12 mg. per 100 cc. On December 14, basal metabolism −39. January 8 blood calcium, 8.8; urea nitrogen, 11.2; creatinin, 1.6 mg.; cholesterol, 0.557 per cent; March 1, 1929, basal metabolism −10; blood sugar, 0.094; urea nitrogen, 16.3; cholesterol, 0.292 (this was following several months of thyroid extract and high-protein diet treatment).

This patient was here under observation for five months. At first diuretics were tried, but to no avail, so that a week or two after her admission she was put on a high-protein diet. This consisted of protein, 120; fat, 50; carbohydrate, 120. Also she was given 5 grains of thyroid extract per day. She began to lose weight and the edema began to disappear, so that one month later her weight was 169 pounds, showing a loss of 40 pounds. Her blood pressure remained low and she developed no anemia during her stay. The thyroid extract then was reduced to 1 grain daily. The patient immediately began to develop edema and gained weight again. During the whole time she was here the proteins were kept up to a level of about 120 gm. During the period in which the thyroid extract was cut down to 1 grain per day, I gave her parathyroid (Collip's) for one week, during which time the patient gained a pound per day. The week following this, on discontinuing the parathyroid, she was tried on calcium chlorid, 12 gm. per day. She gained a pound per day also on this treatment. The thyroid extract was then raised to 3 grains per day, during which time she continued to gain weight slowly until she reached 196 pounds again. Then for some unknown reason, and without changing the medication or treatment, she began to improve. The edema decreased and she was finally discharged, weighing 160 pounds. Her diet at discharge was protein, 120 gm.; fat, 50; carbohydrate, 120. Medication—thyroid substance 3 grains daily.

**Case Summary.** This case also answers to all the requirements of nephrosis. Unfortunately we have no apparatus at present for the detection of the double refractile bodies, so that they are not given in any of these cases. This patient improved on the thyroid extract and high protein. She seemed to grow worse on parathyroid (Collip) and calcium chlorid. The cyclic character of the disease was apparent, however, in this case. She showed relapses and remissions when the medication was not changed. The final improvement was marked and we expect to follow this case to its conclusion.

Case III.—(26555R) a female, aged thirty-nine years, occupation, clerk in a bank. Was admitted September 24, 1928. Complaint, kidney trouble.

She described a general bloating of the body which began in the feet about two months prior to admission here. She speaks of being unusually tired since last spring. She was examined for insurance six months prior to coming here and pronounced well except for diseased tonsils, was passed for insurance also a year ago. Thinks her whole sickness dates from a severe cold beginning about July 4, 1928. She had been accustomed to have a great many colds in the head. Past illnesses—measles, mumps, scarlet fever in childhood. Married three years, no pregnancy. Patient worked very hard in the bank in the day time and took correspondence courses at night. Family history negative.

Physical examination on admission showed her blood pressure 118 systolic and 70 diastolic, considerable puffiness around the eyes and face and marked edema of the legs and ankles. Tonsils diseased. There was a slight thyroid adenoma. Remainder of the examination negative.

Fluoroscopic chest examination was normal. Dentograms were normal. Blood count showed erythrocytes, 4,700,000; leukocytes, 11,200; hemoglobin, 80 per cent; neutrophiles, 81.4 per cent; lymphocytes, 17.3 per cent; eosinophils, 1 per cent; basophils, 0.3 per cent (patient had a severe cold at this time). Urinalysis showed albumin ++; occasionally finely granular and hyaline casts, many erythrocytes and many leukocytes. The phthalein test showed 66 per cent for the two hours. The specific gravity of the urine varied from 1.007 to 1.023. Blood sugar was 0.082 per cent; urea nitrogen, 10.8 mg. per 100 cc. Blood cholesterol, 0.596 per cent; total serum protein, 4.92 per cent; serum albumin, 2.36 per cent; serum globulin, 2.56 per cent; total nonprotein nitrogen 23.6 mg. per 100 cc. Blood Wassermann was negative.

At first the patient was thought to be an acute nephritic and placed on a special diet low in protein. She seemed to improve a little but this was probably due to the fact that she was kept in bed. The edema, however, only improved slightly. On October 8, the tonsils were removed. At this time the important factors in the case were marked edema and marked albuminuria with no increase in blood pressure and no retention of nitrogen in the blood. She also had an oliguria and the specific gravity of the urine was high. There were, however, erythrocytes and casts in each specimen, which seemed to complicate matters, but on finding the high-blood cholesterol and the reversed ratio of globulin, we decided that this was a case of nephrosis.

She was very sick after tonsillectomy and the edema grew worse. On October 14, we gave her 100 gm. of protein per day but on account of her poor appetite she could not eat all of this. This patient left on October 27, about a month after coming here, and was little, if any, improved from her condition when she entered. No thyroid extract was given to this patient.

Several letters from her since report no improvement. I do not believe she keeps up the high-protein diet and have advised her physician to carry on with large doses of thyroid extract and also with the high-protein diet.

**Case Summary.** I believe this case to be a mixture of nephritis and nephrosis. There were casts and red blood cells in all specimens of urine. The onset was rather sudden following an acute cold. On the other hand, the blood pressure was low, there was no nitrogen retention in the blood, and the kidney function tests were good. Also the blood cholesterol was very high and there was an inversion of the albumin globulin ratio. She reports no improvement, but she discontinued her high protein at home and to date has been given no thyroid extract.

Case IV.—(12607) a male, aged forty-five years, occupation, bookkeeper. Admitted October 15, 1923. Complaint swelling of the legs, shortness of breath, weakness.

This patient had not been well since an attack of influenza in 1920. In the spring of 1923, he noticed his ankles were swelling and in July, 1923, was obliged to give up work because of weakness and shortness of breath. The family history was negative. The patient was married and had one boy and one girl, both healthy. His habits had been normal. His past illnesses included measles and scarlet fever thirty years ago. In 1920, he had severe influenza. The edema had been very marked since the previous May.

On physical examination the patient was bedridden, had marked edema of the legs, his blood pressure was 158 systolic and 110 diastolic. The edema extended up over the back and abdomen. The heart was regular with no murmurs. There was free fluid in the abdomen.

The urine coagulated thick. There were innumerable hyaline, waxy and finely granular casts. There were occasional erythrocytes and many leukocytes. The phthalein was 41 per cent for the two hours. The specific gravity of the urine varied from 1.030 to 1.045. The same urine picture obtained in all specimens except for the absence of red blood cells in most specimens. The blood Wassermann was negative. The blood count showed erythrocytes, 4,220,000; leukocytes, 8,400; hemoglobin, 90 per cent; neutrophils, 48 per cent; lymphocytes, 48 per cent; transitionals, 1.6 per cent; eosinophils, 1.6 per cent; basophils, 0.8 per cent. Blood sugar, 0.125 per cent; phosphates, 4.85 mg. per 100 cc.; calcium, 9.1, uric acid, 3.8; urea nitrogen, 21; creatinin, 1.2 mg. per 100 cc.; plasma bicarbonate, 52 volume per cent.

This patient had been on a salt-free, low-protein diet but on October 24 he was put on one high in protein. When he left for home two weeks later there was no improvement.

Patient returned in October, 1924. During the intermission he had continued on a full protein diet with gradual improvement so that by January 1, 1924, he was out of bed and by April he was able to go fishing and boating. By July, he was back at work again without any distress of any kind. On admission in October his blood pressure was 146 systolic and 84 diastolic. The edema had disappeared with the exception of some slight pitting along the shin bones. The urine still coagulated solid, however, and still showed granular, waxy and hyaline casts. The kidney studies showed marked deterioration. The phthalein was only 6 per cent for the two hours. Blood sugar was 160; plasma $Co_2$, 40 volume per cent; urea nitrogen, 35; uric acid, 5.8; creatinin, 2.1 mg. per 100 cc.; cholesterol, 0.319 per cent.

It was decided that there was a decided mixture of nephritis in this case and that the high protein was irritating the kidneys so that he was allowed to go home and cut down on the protein. He returned again in May, 1925. In the meantime, he had been eating a balanced diet and stated that he had been gradually improving. He had been working every day and felt fine until about two weeks prior to returning, when he complained of feeling "dopy." At this time his blood count showed erythrocytes, 3,470,000; leukocytes, 11,200; hemoglobin, 61 per cent; neutrophils, 71.3 per cent; lymphocytes, 23.7 per cent; large monos, 2.3 per cent; eosinophils, 2.6 per cent; basophils, 0.2 per cent. The urine still showed the same picture, coagulating solid. There were red blood cells present with casts. Urea nitrogen was 23.8 mg. per 100 cc., the blood cholesterol was 0.319 per cent. Ten days later, while at home, this patient had a convulsion and died in a few minutes.

*At autopsy*, the kidneys measured about 8 by 4 by 3 cm. The capsules stripped with difficulty. The surface was very granular and reddish gray in color. On section, the cortex in some places was not more than 1 mm. in width, and not more than 3 mm. at points of greatest width. The

striations were entirely lost. Microscopically, they showed marked increase in fibrous connective tissue throughout the entire cortex. In many areas there was diffuse cellular infiltration and occasional clumps of lymphocytes. The tubules for the most part were dilated and lined by low cuboidal epithelium. In some places there was granular débris filling the tubules and in other places a castlike substance. The glomeruli were replaced by fibrous connective tissue.

**Case Summary.** This case appears to be a mixture of nephritis and nephrosis. At first the nephrosis seemed to predominate and to improve on high-protein diet, so that from a bedridden condition he was able to return to work. He developed a renal insufficiency ultimately and died as a result.

**Conclusions.** Pure cases of lipoid nephrosis are rare. They constitute a real and definite entity, however, and are amenable to treatment. We have here reported 2 cases of "genuine nephrosis" and 2 mixed cases, one of which came to autopsy. Of the 2 "true" cases, one is cured and one improved on treatment.

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# SIX FATAL CASES OF DIABETIC ACIDOSIS.

## With Special Reference to the Occurrence of Acute Pancreatic Necrosis in One and Severe Nephrosis in Another.

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Nine cases of diabetic coma were studied at the Cook County Hospital this year, with the particular purpose of investigating a series of diabetic acidoses of the type which is fatal in spite of treatment according to an accepted program. All of them, although complicated, fell properly into the class of diabetic acidoses when measured by a combination of the usual clinical and laboratory criteria. All were poor risks at the start; 4 recovered and 5 died.

The benign cases are not detailed since their recovery was in no wise remarkable. The complications may be noted: One was complicated by an extensive and acute membranous sore throat, not diphtheritic; a second by a subacute purulent otitis media and chronic malaria; a third by a huge carbuncle of the neck. The fourth case was complicated by a latent thyrotoxicosis, and entered again later to become one of our "fatal" group (Case I). It may be further noted that despite such handicaps, these patients gave prompt clinical and chemical evidence of good response to treatment.

The fatal cases are here presented, together with one other similar case not in the series, but included because of its unusual kidney lesions. They represent a group of fatal diabetic acidoses in which clinical data combine with necropsy findings on 5 of the 6 cases to throw light on their failure to recover under treatment.

All cases were handled on a similar régime. Insulin was given every six hours. Glucose was administered as milk, orange juice or sugar and water, by mouth, or subcutaneously in 5 per cent solution, or intravenously in 50 per cent solution. Alkalies were given in 4 instances. Fluids, gastric lavage, external heat, enemata and stimulants completed the therapeutic armamentarium. Dosage is indicated on Charts I and II. Blood chemistry determinations were made at the beginning of each period.

Intravenous alkali, when used, was given in 5 per cent solution, 15 gm. of sodium bicarbonate and 0.3 gm. of potassium bicarbonate being dissolved in 300 cc. warm double distilled sterile water immediately before infusion. After a few cubic centimeters of clear water this was followed by 5 cc. of 5 per cent calcium chlorid. This combination of salts was suggested by Dr. R. W. Keeton, of the

College of Medicine of the University of Illinois, as being one which would approach a replenishment of depleted alkali in something like physiologic proportions. The injections were made by a gravity apparatus and were prolonged over forty-five to sixty minutes.

Blood sugar was determined by the Folin-Wu method, blood plasma carbon dioxid combining power by the Van Slyke method, urine sugar by Haynes and Benedict's methods and acetone bodies by the nitroprussid and ferric chlorid tests.

For anatomic descriptions and their interpretation I am indebted to Dr. R. H. Jaffé, pathologist of Cook County Hospital.

**Case Summaries.** CASE I.—*Diabetes and Thyrotoxicosis.* A white woman, aged thirty-two years, suffering with diabetes and thyrotoxicosis, entered the hospital six times.

On her *first admission*, October 3, 1927, she complained of weakness, nervousness, excessive perspiration, palpitation, polyphagia, weight loss from 185 to 110 pounds and exophthalmos which had been present one year, starting with an obscure febrile illness of three months' duration. *Examination* at this time revealed a thin, pale woman with normal temperature; pulse, 120; respiration, 36; blood pressure, 130 systolic and 85 diastolic. Exophthalmos, cardiac hypertrophy, a systolic murmur at the apex and an enlargement of the thyroid were noted. There was glycosuria but no acetonuria. The basal metabolic rate was +35. The thyrotoxicosis was not treated; the glycosuria was controlled without insulin on a diet of carbohydrate, 65; protein, 65; fat, 100.

Subsequent to this, and prior to her final entry, the patient went into typical diabetic coma five times; four times she was treated at Cook County Hospital, and the essential data of these admissions is summarized in Chart I. The respective dates of these entries were: February 2, 1928; October 10, 1928; January 11, 1929; March 11, 1929. During the entire period she evaded any careful management. The prodromal symptoms of her coma were each time the usual headache, stupor and vomiting, varying irregularly from one to seven days in duration, and each time she recovered promptly, only to leave the hospital before diet and insulin could be properly adjusted. Further readings of the basal metabolic rate were +92 in February, and +82 in March, 1928, but surgical treatment of the condition was not urged and Roentgen ray treatment was refused.

Her *final admission* was on May 19, 1929. She had been feeling fairly well up to twelve hours before entry, when she complained only of headache; a few hours later she was discovered in coma. On *examination* the temperature was 97° F.; pulse, 80, and almost imperceptible; respirations, 20; blood pressure, 70 systolic and 40 diastolic; weight, 50 kilos (estimated). She was irrational, able to swallow, but not to answer questions, and her respirations were sighing and groaning, but not so deep or frequent as is typical of diabetic coma. There was an acetone odor to the breath, the skin was dry and the face pink, exophthalmos and the goiter were still present. Scattered crackles were heard at the right lung base, and there was a palpable friction rub over the anterior right chest. Glycosuria, acetonuria, hyperglycemia and a lowered blood carbon dioxid confirmed the *diagnosis* of diabetic coma. *Treatment* was instituted and is summarized on Chart I. She appeared to rouse from her stupor at the beginning, but soon the signs of a pneumonia developed at the right base; the patient sank into a toxic state, and in spite of all therapy she died the next morning.

*Necropsy.* The chief findings were atrophy of the pancreas, hypostatic confluent bronchopneumonia of both lower lobes and a nodose colloid

goiter with central fibrosis. The pancreas was moderately firm with fairly distinct lobulations. Microscopically there was a marked increase in the interlobular fat tissue, and many fat cells invaded the lobules. There was a metaplasia of the epithelium of some of the larger ducts. Small areas of atrophy of the acini occurred in the center of the lobules. The islands were scanty, and although those present were all preserved, they were occasionally rather small. Additional findings were fibrous obliteration of the right pleural cavity, cloudy swelling of the myocardium, fatty changes and parenchymatous degeneration of the liver; acute inflammatory reaction of the spleen with anemic infarct, slight atheromatosis of the aorta, decreased lipoid content of the adrenal cortices, multiple follicular cysts of the ovaries and chronic erosive cervicitis with multiple subepithelial abscesses and cysts.

CASE II.—*Diabetic Coma, Pulmonary Tuberculosis and Unexplained Convulsions.* A white man, aged forty years, entered the hospital in deep coma. The only *history* available was that he had had diabetes for one year, that he had been up and about until the night before, and that a physician noted both glycosuria and convulsions several hours before entry. On *examination* the temperature was 97° F.; pulse, 120; respirations, 26; blood pressure, 98 systolic and 78 diastolic; weight, 50 kilos (estimated). The patient was small, lightly built, emaciated, dehydrated and in complete coma. Generalized clonic convulsions occurred every fifteen minutes, lasting one to two minutes, and eventuated in periods of apnea of about thirty seconds. The skin was dry and scaling, there was an acetone odor to the breath, and the breathing was very weak and shallow. There was neither choked disk, retinitis nor any evidence of middle-ear infection to suggest an explanation of the convulsions. Reflexes were absent. Urine showed sugar, acetone, albumin and casts. The spinal fluid was normal. *Diagnosis* was somewhat doubtful: Severe diabetic acidosis seemed certain and was confirmed by the blood chemistry reports (Chart I), but uremia, cerebral accident and insulin shock were likewise considered as a possible basis of the convulsions. *Treatment* was started, but was ineffective; the convulsion continued and death ensued in four hours.

*Necropsy* confirmed the diagnosis of diabetes, but revealed some unsuspected lesions. The chief findings were atrophy of the pancreas, ulcerous pulmonary tuberculosis of the right upper lobe with a healed primary lesion of the left lung and bilateral obliterative pleural adhesions and fibrocaseous tuberculosis of the tracheobronchial lymph nodes; primary contracted kidneys with fatty changes and cloudy swelling; and purulent seminal vesiculitis. The pancreas was slightly softer than normal, with a moderate increase in the interlobular and intralobular connective tissue. There were small areas of atrophy of the parenchyma. The acinar cells contained much fat and the medium-sized arteries were infiltrated by lipoid material. The islands of Langerhans could not be discerned. The brain was both macroscopically and microscopically normal. Additional findings were extensive atheromatosis of aorta and coronaries; eccentric hypertrophy of the heart with dilatation; brown atrophy and parenchymatous degeneration of the myocardium; mucopurulent tracheobronchitis; acute infectious splenic tumor; cloudy swelling, brown atrophy and fatty changes in the liver.

CASE III.—*Diabetic Coma and Ischiorectal Abscess.* A negress, aged forty-nine years, entered the hospital on May 6, 1929, in moderately good condition, complaining of pain in the rectal region of one week's duration, which for three days had been associated with constipation. For many months she had had a nocturia of about six times nightly. *Examination:*

Temperature, 102.6° F.; pulse, 118; respirations, 24; weight, 100 kilos. The patient was an obese, colored female, with no remarkable findings other than a left ischiorectal abscess, which was opened and drained some 10 cc. of pus. By evening she was very thirsty and an acetone odor was noted on the breath.

*Status when seen by us at* 10.30 P.M.: Temperature, 98.4° F.; pulse, 180; respirations, 36; blood pressure, 200 systolic and 100 diastolic. She was semistuporous, but could swallow and would answer questions; there was mild dehydration and acetone breath; respirations were weak and shallow. Glycosuria and acetonuria, hyperglycemia and a lowered blood alkali were present. The *diagnosis* appeared to be diabetic acidosis complicated by intoxication from the abscess and hypertension. The general condition did not at first seem alarming, but the response to *treatment* was poor. A little mental brightening and an improvement in the pulse ensued upon the administration of the alkali, but the respirations became constantly feebler and more rapid, the pulse became imperceptible, the skin become cold and moist and she died within seventeen hours from the beginning of intensive treatment, although laboratory reports indicated that the metabolic disturbance had been in large part corrected. Data is on Chart I.

*Necropsy.* The findings were those of a generalized sepsis, with a general softening of the internal organs, acute infections of the spleen, and a large abscess of the left gluteal region. The pancreas weighed 112 gm., and was soft; microscopic sections were not made. Additional findings were hypertrophy and degeneration of the myocardium, cloudy swelling of the kidneys, congestion, emphysema and edema of the lungs and nodose goiter.

CASE IV.—*Diabetic Coma and Gangrene.* A negress, aged forty-nine years, entered the hospital on May 4, 1929, complaining of pain and discoloration of the right foot which had been present for ten days following the "picking" of a corn. Glycosuria had been discovered two weeks before. On *examination*, she was not acutely ill; the dorsum and toes of the right foot were involved in a dry gangrene. The patient was treated by diet and heat to the foot, but sank gradually into stupor.

*Status when seen by us on* May 6: Temperature, 97.6° F.; pulse not perceptible; apex beat, 80; respirations, 20; blood pressure, 80 systolic and 60 diastolic; weight, 60 kilos (estimated). The general condition was obviously poor; the coma was complete, with no response to questions, inability to swallow and absent reflexes; there was moderate dehydration and the breath was foul. Moderate glycosuria and acetonuria were present, along with a marked hyperglycemia and a definitely lowered blood carbon dioxid. *Treatment* was completely ineffective, and the patient died the next day. The data is summarized on Chart I. Necropsy was not permitted.

CASE V.—*Diabetic Coma and Acute Pancreatic Necrosis.* A colored man, aged twenty-eight years, entered the hospital on March 25, 1929, in deep stupor. The *history* was obtained from the wife and told of an illness of two weeks' duration with indefinite onset; the chief complaints were abdominal discomfort, described as a full "drawing" pain in the left epigastrium which was constant but not acute; vomiting occurred almost daily, usually after food, with blood flecks noted once; anorexia alternated with polyphagia; occasionally large meals were retained. Polyuria and polydipsia were noted for about one week. Constipation had existed for two days, but had been relieved by enemas. Previously the patient had always been healthy; he had used alcohol moderately. *Examination* on entry revealed a powerfully built, obese young negro, with temperature, 100.2° F.; pulse, 116; respirations, 56; blood pressure, 86 systolic and 50 diastolic; weight was estimated at 100 kilos. He was completely relaxed, unable to respond

CHART I. CASES I-II-III-IV

| CASE NUMBER | RESULT | NO. OF HRS. TO DEATH OR RECOVERY | URINE | | | | BLOOD | | | TOTAL FROM BIGINNING TREATMENT TO RECOVERY OR DEATH. | | | | | REMARKS |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | SUGAR | ACETONE | DIACETIC | SUGAR | $CO_2$ VOLS % | UREA N | INSULIN UNITS | GLUCOSE GMS. | FLUIDS | ALKALIES | OTHER THERAPY | |
| I Admission 2 | Recovery | 16 | on Entrance | 6.6% | ++++ | ++++ | 375 | 24 | | 180 | 70 | 700 c.c. Orangejuice | 2.0 gm. oral (Na $HCO_3$, Na Acetate, K Citrate) | | |
| | | | on Recovery | 0 | Trace | 0 | | | | | 21 | 300 c.c. Milk | | | |
| Admission 3 | Recovery | 7½ | on Entrance | ++++ | ++++ | +++ | 300 | 24 | | 125 | 39 | 240 c.c. Water<br>390 c.c. Orangejuice | 6.0 gm oral (NaHCO3, Na Acetate, K Citrate) | caffeine 0.3 gm. q. 1 hr. x 6<br>S.S. enema<br>gastric lavage | |
| | | | on Recovery | Trace | ++ | + | 136 | 44 | | | | | | | |
| Admission 4 | Recovery | 16 | on Entrance | ++++ | +++ | | 600 | | | 170 | 125 | 250 c.c. Milk | 20.0 gm oral (Na $HCO_3$, Na Acetate, K Citrate) | gastric lavage | |
| | | | on Recovery | ++ | Trace | | | | | | | | | | |
| Admission 5 | Recovery | 14½ | on Entrance | 1.25% | ++++<br>+++ | ++++ | 556 | 22 | 9.8 | 110 | 20 | 1000 c.c. Saline (Hypodermoclysis)<br>1200 c.c. Water + Sugar | | external heat<br>S.S. enema | |
| | | | on Recovery | 0.5% | + | 0 | 315 | 30 | | | 98 | 1400 c.c. Milk | | | |
| Admission 6 | Death | 31 | on Entrance | 1.25% | ++++ | +++ | 500 | 25 | 13.5 | 170 | 140 | 1600 c.c. Saline (H)<br>1800 c.c. Water<br>2000 c.c. Milk | 15.0 gm. $NaHCO_3$<br>0.3 gm K $HCO_3$<br>oral | external heat<br>S.S. enema<br>adrenalin 10cc x3<br>caffeine 0.3 gm. x4<br>digalin 20cc x 2 | clinically out of coma for short time about 6 hours after entry |
| | | | on Recovery | trace | ± | 0 | 566 | 24 | | | | | | | |
| II | Death | 4 | on Entrance | + + | +++ | trace | 628 | 26 | 16 | 50 | | 1600 cc. Saline (H) | | external heat<br>S.S. enema<br>caffeine 0.5 gm.<br>adrenalin 1.0 cc | |
| | | | Before death | 2.5% | Trace | 0 | 640 | 20 | | | | | | | |
| III | Death | 16½ | on starting treatment | 3.0% | ++ | ± | 500 | 32 | | 160 | 68 | 3600 c.c. Saline (H)<br>800 c.c. Milk + Sugar<br>300 c.c. Alkali (I.V.) → | 15.0 gm. $NaHCO_3$<br>0.3 gm. $KHCO_3$<br>0.25 gm. $CoCl_2$ | external heat<br>caffeine 0.3 gm. x10<br>gastric lavage | vomited some of milk; last blood chemistry 10 hours before death |
| | | | before death | Trace | ± | 0 | 365 | 40 | 42 | | | | | | |
| IV | Death | 15¾ | on starting treatment | ++++ | +++ | + | 500 | 26 | | 200 | 40 | 2400 c.c. Saline (H)<br>400 c.c. glucose and alkali (Intravenous) → | 15.0 gm. $NaHCO_3$<br>0.3 gm. $KHCO_3$<br>0.25 gm. $CoCl_2$ | caffein 0.3 gm.<br>x 9 | |
| | | | before death | ++++ | ++ | ± | 500 | 28 | | | | | | | |

to questions or to swallow, with Kussmaul breathing, acetone breath and dry skin and mucosa. The lungs were clear. The abdominal wall was thick, firm and muscular, but relaxed and only moderately distended. No masses nor organs were felt and the percussion outlines were normal. Glycosuria and acetonuria were moderate; hyperglycemia and depletion of the blood alkali were marked; the white blood count was 12,500 and the blood and spinal fluid Wassermann reactions returned negative. The *diagnosis* of diabetic coma seemed probable, and when the temperature rose to 103° F. and vomiting persisted in spite of gastric lavage, a peritonitis was suspected. Although *treatment* was unsuccessful, there was a remarkable brightening following immediately upon the intravenous alkali, when the patient woke up, asked where he was and said he felt better. However, in ten minutes he lapsed back into stupor and died within ten hours from entry. The data are summarized on Chart II.

*Necropsy.* The essential findings were an acute necrosis of the pancreas with extensive fatty necrosis of the peritoneum. There were, in addition, a fatty infiltration of the liver, parenchymatous degeneration of the myocardium, infectious softening of the spleen, petechial hemorrhages of the gastric mucosa, hemorrhagic bronchopneumonia of both lower pulmonary lobes and slight eccentric hypertrophy of the heart.

The *pancreas* weighed 370 gm. and measured 20 by 6 by 3 cm. The capsule was covered by a thin fibrous membrane, and there were numerous necrotic areas on its surface, on the cut surface and in the surrounding fat tissue. Microscopy demonstrated these areas of necrosis to involve the parenchyma and the interstitial fat tissue. They were surrounded by zones of capillary hyperemia. There was swelling of the fibrocytes and loose accumulations of white blood cells. Outside of the necrotic areas there was a slight increase of the interstitial tissue. The islands were well preserved.

Case VI.—*Diabetes, Pneumonia and Severe Nephrosis.* A white woman, aged thirty-seven years, a housewife, entered the hospital on October 17, 1928. She had been irrational for six hours. Previously, she had been for several weeks on a poorly controlled régime of diet and insulin for diabetes. *Examination* on entry showed a thin, pale woman with temperature, 98.2° F.; pulse, 118; respirations, 32; blood pressure, 122 systolic and 86 diastolic. She was confused, but could swallow and answer questions; respirations were deep and sighing. Glycosuria was marked, and acetonuria mild. A *diagnosis* of diabetic coma was made and she was treated as is detailed on Chart II.

The course was apparently puzzling. An original improvement was followed by a severe insulin reaction, and this by a confused mental state which persisted until she sank into coma again and died on the seventh day. Lung involvement was not suggested or suspected. Acetonuria disappeared promptly and did not return with the coma.

*Necropsy.* The chief findings were a chronic interstitial pancreatitis; a pneumonic process in the right lower and middle lobes with one small abscess; and a severe nephrosis. Additional findings were softening of the heart and spleen, sclerosis of the aorta and coronaries, bronchitis of the left lower lobe and decreased lipoid in the adrenal cortices. Microscopically, the pancreas showed a diffuse increase of interstitial connective tissue and loose accumulations of leukocytes, lymphocytes and histiocytes. The islands were very scanty and those which were present were very small and composed of cells which were dark, nucleated and showed hyalin degeneration.

The kidneys were large, smooth and light yellow, with an irregular network of thin purple strands. The capsule stripped easily. On the cut

CHART II - CASES - V and VI

| CASE NUMBER | DATE and TIME | URINE | | | | | BLOOD | | | INSULIN | GLUCOSE | FLUIDS | ALKALIES | OTHER THERADY | REMARKS |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | AMOUNT | SUGAR | ACETONE | DIACETIC | ALBUMEN | SUGAR | $CO_2$ Vols % | UREA N | UNITS | GRAMS | | | | |
| V | 3-25-29 12:00 noon | 500cc | 1.66% | ++++ | + | + | 600 | 16 | | 15 | | 2400cc saline (Hypodermoclyses) | | external heat | |
| | 2:00 P.M. | | | | | | | | | 35 | 24 | 200 c.c. milk & sugar | | gastric lavage caffein 0.3 gm | gastric contents 300 c.c. brown fluid; Benzidene (-) |
| | 4:00 P.M | | | | | | | | | | 21 | 300 c.c. milk | | S.S. enema | |
| | 6:00 P.M. | complete 5 c.c. | ++++ | +++ | 0 | ± | 500 | 18 | | 50 | | | | caffein 0.3 gm. | milk given but all vomited. |
| | 8:00 P.M. | | | | | | | | | | 40 | ← 200 c.c. 20% glucose } Intravenous 300 c.c. alkali } → | 1.5 gm. $NaHCO_3$ 0.5 gm. $KHCO_3$ 0.2 gm. $CaCl_2$ | adrenalin 1.0 c.c. | momentary brightening |
| | 10:00 P.M. | complete 10 c.c. | ++ | 0 | 0 | | 588 | 38 | 51.8 | | | | | | died; data immediately antemortem. |
| VI | 10-17-28 consec- I | | ++++ | + | + | + | 488 | | 28.9 | 100 | 30 | water ad lib and with sugar throughout | $NaHCO_3$ Na acetate K citrate } aa 10.0 gm. oral | caffein 0.3 gm. x 4 gastric lavage | |
| | utive II | | ++++ | 0 | 0 | + | 318 | | | 80 | 60 | | | | clinically improved |
| | 6-hour periods: III | | ++++ | 0 | 0 | + | | | | 70 | 60 | | same — aa 15.0 gm | | |
| | 12M-6 A.M. etc. IV | | ++++ | 0 | 0 | + | 286 | | | 100 | 30 | 1600 c.c. saline (H) 300 c.c. orange juice | | | |
| | 10-18-28 I | | +++ | 0 | 0 | + | | | | 50 | 30 | 200 cc orange juice + sugar | same — aa 12.0 gm | | emesis |
| | II | | ++ | 0 | 0 | + | 42 | | | 50 | 30 | 200 c.c. orange juice + sugar | | | |
| | III | | 0 | 0 | 0 | + | 28 | 3:00 P.M. | | 20 | 50 | 300 c.c. orange juice + sugar | | | conscious |
| | IV | | | | | | | | | 20 | 20 | | | adrenalin 1.0 c.c. | insulin coma — 3:00 P.M. recovered — 4:30 P.M. |
| | 10-19-28 | | ++++ | 0 | 0 | + | | | | 100 | 56 | 800 c.c. milk | | | irrational |
| | 10-20-28 | | ++++ | 0 | 0 | + | | | | 120 | 112 | 1600 c.c. milk | | | conscious; complaining abdominal pain |
| | 10-21-28 | | ++++ | 0 | 0 | + | | | | 100 | 112 | 1600 c.c. milk | | | very restless |
| | 10-22-28 | | ++++ | 0 | 0 | + | 425 | | | 275 | 133 | 400 c.c. milk | same — aa 12.0 gm | | clinically seems quite well |
| | 10-23-28 | | ++++ | 0 | 0 | + | 460 | | 72 | 60 | 50 | | | | back in coma |
| | | | | | | | | | | | | | | | died 8:00 P.M. |

surface the tissues were swollen and the pyramids poorly differentiated. Parallel to the border, in the cortex was a distinct whitish yellow line, 1 to 2 mm. thick. The outstanding microscopic features were a very marked edematous loosening of the stroma and a dilatation of the convoluted tubules. In the stroma the connective-tissue fibers were spread apart by a pale stained substance. The fibrocytes were swollen. There were occasional small perivascular accumulations of lymphocytes. The epithelium of the convoluted tubules was low cuboidal and in many of the cells were large and small vacuoles which did not take the fat stain. There was very little fat in the epithelium. The lumen was empty, or contained a foamy network of pale-stained granular material. The glomeruli showed a slight sclerosis of the tufts, but there was no swelling nor proliferation of the tuft cells. The afferent arterioles had a slightly thickened hyalin wall.

**Discussion.** In considering the group of cases as a whole, our first interest lay in discovering why they did not respond to treatment. Three reasons suggest themselves: (1) They might have been already overwhelmed by the process of acidosis when first seen; (2) they might have been suffering from a complication which so inhibited the power of insulin as to let the disease proceed as though untreated with this remedy (the familiar "insulin-resistant" diabetic); or (3) they might have been suffering from a complication itself fatal. Very roughly, and with overlapping, our 5 cases permit themselves to be considered as presenting three fairly distinct clinical pictures in which one or the other of these elements predominates.

Cases II and IV seem to fall properly into the first class. They were in a state of complete relaxation, unable to talk or swallow or understand, with abolition of reflexes, incontinence of urine and subsidence of Kussmaul respiration. This picture may be interpreted as a toxic exhaustion; patients once exhibiting it seem not to respond to any type of therapy. Whether this depression was due here to the acidosis rather than to the toxicity of the complicating process—ulcerative tuberculosis and gangrene respectively—is not certain. Neither showed the slightest response of any kind.

Case I comes under the second heading. Infection is an accident, which in any stage of diabetes, but especially in coma, is well known to interfere with the potency of insulin. Such interference is not always grave. However, it would appear that in Case I a pneumonic process, itself rather mild, nevertheless made it impossible to restore the patient to a normal metabolism and normal acid-base equilibrium. Examination of her records for testimony as to the inhibiting effect of the infection on insulin in her final entry discloses the following data: (1) Therapeutic régimes in all admissions were roughly similar. (2) On no other entry was there evidence of infection. (3) Symptoms of acidosis had not persisted longer in the final than in previous instances. (4) Laboratory findings infer metabolic derangements of about equal severity in all entries. Definite glycosuria and acetonuria were present each time;

blood chemistry readings are indicated on Chart I. (5) No obvious malignant factor appears in the final entry other than the infection. (6) Amount of insulin used to no benefit in the fatal entry was as great as that found to be effective four times previously. Data on Chart I.

One may reasonably conclude from all this that the mild early pneumonia, which was demonstrated at autopsy to exist at the time of the patient's death, caused a fatal outcome more through its inhibition of insulin than through its own toxicity.

It is interesting to note that the work of Lawrence[9] suggests that the mechanism by which infection inhibits insulin may be through thyroid and adrenal stimulation. In this case we have clinical evidence of thyrotoxicosis from the time of her first entry. A basal rate in 1928 was +92 per cent. Although this overactivity of the thyroid was not apparently antagonistic to insulin in the previous entries in coma, it is possible that when the thyroid was further stimulated by the infection it was a significant factor in the fatal outcome. The question is also raised, whether the ease with which the patient developed severe acidosis may have been as much dependent on her doubly deranged metabolism as on her therapeutic negligence.

Finally, Cases III and V furnish examples of complicated diabetic coma, in which death seems rather to be due to the complicating factor than to the acidosis. The blood carbon dioxid levels were brought up to 40 and 38 respectively, the chemical and clinical signs of acidosis were relieved, and the patients died in a toxic state. Existence in Case V of an acute pancreatic necrosis will be further discussed; Case III, although showing locally only a large ischiorectal abscess, gave postmortem evidence in the state of the other organs, of a generalized sepsis. The question of how far the diabetes aggravated the complicating pathology cannot be answered. Certainly acute pancreatitis often kills even without causing a marked upset of carbohydrate metabolism, and a large abscess may even in a normal person precipitate a fatal septicemia. Case VI, with its pneumonia and lung abscess, probably belongs with these.

**Results of Alkali Administration.** In turning to the results which followed on the use of alkalies in 4 of these cases, it is obvious that there was *a priori* not much to be expected from such medication. The original blood carbon dioxid reading, whatever its value in reflecting the state of acid-base equilibrium in the body, was above the fatal level in all instances: 32, 26, 25 and 16 volumes per cent. The patients were no doubt as ill from toxins as from depleted base, and the probable value of rapidly increasing the alkali reserve was at best questionable. One observation seemed to justify the attempt. There was in all these cases an acetonuria which was very slight in proportion to the degree of acidosis implied by the blood carbon dioxid findings. This suggested that these cases might have

an element of nonketone acidosis in them,[1,13] and that alkali administration might be particularly indicated in their treatment.[1,4,10,13] Unfortunately, neither our clinical results nor the chemical determinations admit of any conclusions about this point. It seems more likely, however, that the failure to excrete significant quantities of acetone bodies in the face of a low alkali reserve resulted in our particular cases from renal and vasomotor insufficiency, rather than from the existence in the blood and urine of unidentified organic acids. The finding of a small or decreasing urinary output in several cases (for instance Chart II) supports this more commonplace interpretation of the low acetone body output.

Our actual results were these: (1) In Case I 15 gm. of alkali by mouth made no change in the carbon dioxid level. (2) In Case IV 15 gm. of alkali intravenously had no greater effect. (3) In Case III, during the six-hour period in which 15 gm. of alkali were given intravenously, the carbon dioxid rose from 32 to 40. But the blood sugar dropped and glycosuria lessened in this same period so that there is evidence that insulin itself was active and might alone account for the slight rise. (4) In Case V, which coincidentally represented the most severe acidosis of the fatal group, during the first six hours the carbon dioxid rose only from 16 to 18 volumes per cent; during the second period, with similar insulin dosage but with intravenous alkali, the carbon dioxid was brought from 18 to 38 volumes per cent. In the same period continued hyperglycemia and glycosuria testify against activity of the insulin.

From this it will appear that there was only 1 case in which intravenous alkali seems to have effected a chemical improvement. The clinical benefit was very temporary. The 2 cases in which alkalies failed to alter the blood chemistry, whatever good one might have expected from such an alteration, may be taken to indicate either that enough alkali was not given, or that there existed a more subtle upset in acid-base balance than one which could be corrected by the simple gesture of pouring in bicarbonate.

**Acidosis and Acute Pancreatic Necrosis.** There occurred among these 6 cases at least 2 rather rare pathologic phenomena. Case V is one of acute pancreatic necrosis in the brief course of which a typical diabetic acidosis developed as a secondary but clinically dominant picture. This view of its pathogenesis is vouchsafed by the absence in the anamnesis of any diabetic symptoms antedating the acute illness, by the patient's state of overnutrition and fair hydration on entry, and by the necropsy findings. Although there is a fairly large number of cases recorded in which diabetes developed sooner or later after proven or inferred pancreatitis, or in which hyperglycemia gave evidence of deranged internal secretion during the period of acute necrosis, only 4 cases are comparable in developing an acute diabetic acidosis simultaneously with the pancreatic

syndrome. The first of these is reported by Caro and Winkler,[2] the second by Rodriguez[11] and 2 others are added by Warfield.[14]

In the 2 cases in which the point is mentioned, 1 reports complete destruction of the islands of Langerhans and 1 their destruction in the midportion and tail. In our own case, in spite of their apparently deranged function, the islands showed good anatomic preservation.

**Nephrosis After Large Insulin Dosage.** The postmortem finding in Case VI of the unusual nephrosis above described suggests a possible relationship between this kidney damage and the huge dosage of 1145 units administered during the six and a half days of treatment. Some degree of nephropathy accompanies almost every severe diabetic acidosis;[3] albumin and casts were found on urinalyses in all these cases, and renal pathology was found in the 5 cases which came to postmortem examination. However, since the opening of the insulin era there has been evidence brought forth suggesting that insulin may at times play a rôle in producing a characteristic renal lesion. On the clinical side there are reports which possibly tend to show some correlation between the amount of insulin given and the degree of nitrogen retention which ensues.[7] On the pathologic side are the reports of somewhat unusual types of renal changes of which our case is an example.

The typical "diabetic kidney" exhibits a nephrosis, characterized by a heavy fatty infiltration of the epithelial cells, and by a storage of glycogen in the epithelium of the loops of Henle in a zone macroscopically visible between cortex and medulla.[5] In contrast to this, at least one observer, Kraus, reports a quite different picture found at section of 3 insulin-treated cases.[8] They developed uremia immediately following their diabetic coma, dying ten, eight and five days after the beginning of treatment for the acute acidosis. (No abnormally large doses of insulin were given.) These kidneys were all greatly swollen, edematous and anemic, with a peculiar yellowish color which gave the macroscopic picture of fatty infiltration. Microscopically, however, there was no fat except that dependent on a lipemia in 1; instead there was a large collection of fluid in the convoluted tubules with a granular and hydropic degeneration of the epithelium and some swelling of the glomeruli. There was also the more usual glycogen zone. It will be seen that, although the author considered the picture a possible early nephritis instead of calling it a nephrosis, these kidneys answer to a description very similar to that of the kidneys in Case VI. Kraus does not himself consider insulin the cause of these changes, but thinks that the appearance of unusual kidney lesions in insulin-treated cases may perhaps be taken to mean that the prolongation of life which insulin makes possible, merely allows the damage due to acute acidosis to develop full blown. The massive insulin dosage in our own case, however, suggests that the hormone itself may in some

way be involved in the production of this renal picture in which the dominant elements are a marked edema involving the stroma, and a hydropic degeneration of the tubular epithelium—a picture similar to that described in chronic dysentery.[6] Such a suggestion must, of course, be made all the more cautiously in so complicated a case, in which the patient suffered not only with diabetes, but with a pneumonic process in the lung.

That the patient was not kept out of coma in spite of the heroic insulin dosage is a fact worthy of comment. Study of Chart II and of the anatomic descriptions affords this probable explanation. The patient was presumably never, after the first few hours, suffering from a diabetic acidosis. The immediate and permanent disappearance of the acetonuria suggests this, as does the pallor which was noted on entry, and which is in sharp contrast to the flushed face of a patient typically affected with ketosis. Further, the continued albuminuria, the rising blood-urea nitrogen and the postmortem findings of a nephrosis and a lung abscess indicate that there was sufficient disease in kidneys and lungs to account for her poor clinical condition. The terminal rise in blood sugar may well have resulted as much from the rather generous feeding of glucose, as from any ineffectiveness of insulin. The occurrence of a reaction forty-eight hours after entry testifies that insulin was active at least at the beginning of treatment.

For permission to report this case I am indebted to Dr. C. J. McMullen of the Medical Department of the University of Chicago.

**Convulsions.** Passing mention in Case II of the occurrence of convulsions may likewise be made. Convulsions in diabetic coma are a symptom infrequently observed. Blood chemistry in the case under discussion tends to rule out both insulin shock and true uremia as their cause. However, the finding of a primary contracted kidney on section reopens the possibility that the convulsions were a manifestation of a general arteriole spasm related to the kidney pathology, rather than a manifestation directly connected with the acidosis. That such an explanation of the convulsions is possible is suggested by Ricker in his discussions of arteriole spasm,[12] more particularly in relation to eclamptic convulsions. The brain was normal.

**Summary.** 1. Six cases of diabetic acidosis, fatal in spite of treatment, have been presented.

2. Clinically, or at autopsy, all these cases were shown to have been complicated by an infective or gangrenous process; 1 of them developed the diabetic syndrome secondary to an acute pancreatic necrosis; 1 of them, treated with huge insulin dosage, exhibited an unusual nephrosis.

3. Analysis of records suggests that death occurred either because treatment was instituted only after intoxication had already progressed too far, or because an infection inhibited the power of insulin, or because the complication was itself fatal.

4. Experiment with the use of 15 gm. of alkali in 4 cases showed significant change in alkali level in only 1 instance and permanent clinical benefit in none.

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## SKIN HYPERSENSITIVITY TO PHENYLHYDRAZIN HYDROCHLORID.

### Report of a Case.

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Recently the subject of hypersensitivity has been stressed in medical literature, and it has been shown that the various tissues of the body may be susceptible to an almost innumerable list of

organic and inorganic substances. Some of these substances, such as the foreign proteins, are commonly recognized, as the cause of either localized or generalized evidences of hypersensitivity.

Others, such as the compound phenylhydrazin hydrochlorid, which not uncommonly causes untoward results when taken internally, must be indeed rare as a cause of reactions following skin contact, since a search of the literature has revealed only one previously reported case. Giffin and Conner[1] recently discussed the results following the internal use of this drug in the treatment of *polycythemia vera*, mentioning the progressive anemia occurring in some patients. Whether this reaction represents a form of true hypersensitivity or not is open to question at present.

The only case of skin hypersensitivity to this compound previously reported was presented by Hall[2] before the British Dermatological Society in 1899. The patient was Scotch, aged thirty years, a research worker in a chemistry laboratory, and first noticed a mild eczema on his fingers in 1894. When he rested from his work, the rash cleared up; when he returned to work in the laboratory, it returned with a constantly increasing severity. He was using phenylhydrazin in a research problem at the time but did not associate that drug with the eczema until a year later when he spilled some on his hand. In two hours he developed an urticarial reaction over most of his body and extremities. He then turned over the work associated with the phenylhydrazin to an assistant. He became progressively sensitive until, according to Hall, on one occasion, when his assistant, who had been working with phenylhydrazin hydrochlorid, came a distance of a mile to see him in his home, he had a severe recurrence of his eczema. The progressive severity of his attacks may be significant from the viewpoint of prognosis in the present case.

Contact with this drug is not limited to a few research workers in the field of medicine today, since practically all freshmen in medical schools use it in the study of the osazones of the various sugars. The occurrence of individuals with a hypersensitivity to it must be rare inasmuch as there appears to have been no cases reported during the present century.

**Case Report.** The patient, male, aged twenty-three years, a medical student, first noticed a mild pruritus of the skin of the thumb and index finger of the left hand, with multiple minute vesicles and diffuse redness over the same area—February 17, 1929.

The next day, February 18, several small red areas, the largest 15 cm. in diameter, appeared on the palmer surface of the hand around the base of the thumb and index finger. Pruritus of the skin of the right thumb and index finger was also noticed. A diagnosis of "dermatitis, probably ringworm" was made by a dermatologist, and a solution of camphor and iodin was prescribed for external application. In the afternoon, the patient worked in the chemical laboratory of the medical college which he was attending.

February 19. The following morning, the eruption was much more severe and it was accompanied by a moderate swelling of the palm, thumb, index finger and ring finger of both hands. Again the patient visited the same dermatologist who diagnosed the condition as "dermatitis, probably of poison ivy or primrose poisoning."

February 21. Both hands, including the palms and all of the fingers, except the fifth finger of the right hand, were so swollen that it was impossible to bend any of the finger joints. The fingers actually appeared to be twice their normal size. There were many broken vesicles with serous contents present and desquamation was moderately severe. Throbbing pains were constant in both hands which incapacitated the patient temporarily. An examination of the urine revealed nothing abnormal. Wet dressings of lead acetate and alcohol were continuously applied without apparent effect.

February 24. A mixture of bismuth subcarbonate, zinc oxide, zinc sterate, glycerin, and carbon detergent, was applied. The condition subsided so rapidly at this time that it seemed doubtful that the relief could be attributed to the medication.

February 27. Both hands had returned to their normal status. The skin appeared to be clear except for a slight residual desquamation. It was then realized that each period of time spent in the chemical laboratory had been followed by an acute exacerbation of the condition. The patient had been an industrial chemist before entering medical school, so it seemed probable that the cause of his hypersensitivity would be found in some element or compound which he was then using but had not used in his previous work.

In the laboratory he was studying the osazones and using in this work phenylhydrazin hydrochlorid (1 part) with sodium acetate (2 parts).

**Experiments.** This fact suggested a series of experiments with two subjects:

A. To determine whether the patient was hypersensitive to phenylhydrazin hydrochlorid plus sodium acetate.

B. To determine what fraction or group of fractions in this compound might be the exciting factor or factors of this hypersensitivity.

1. A few crystals of phenylhydrazin hydrochlorid (1 part) mixed with sodium acetate (2 parts) were rubbed on the volar surface of the left forearm over an area of 1 cm. in diameter. Seven hours later there was marked redness over that area, and at the ninth hour some swelling was noted. Nineteen hours after exposure the redness had extended for a distance of 3 cm. in all directions from the original area and a sharply demarcated elevation of about 2.5 mm. was present over the entire area. Pruritus was marked at first but disappeared after about four days. This was repeated three times with similar results.

2. Phenol (95 per cent) was applied to the skin; until small vesicles appeared, to determine whether the phenol radicle might be the source of the irritation. No reaction followed except for the above-mentioned vesicles which quickly healed.

3. Sodium acetate in powdered form was rubbed in over an area

of several square centimeters on the volar surface of the arm. No skin reaction followed.

4. Hydrochloric acid, concentrated, was applied over an area 1 cm. in diameter on the volar surface of the forearm. No evidence of hypersensitivity was noted.

5. Pure hydrazin hydrochlorid was applied over an area 1 cm. in diameter on the volar surface of the forearm. No evidence of hypersensitivity was noted. This was repeated twice with similar results.

6. Phenylhydrazin hydrochlorid was applied over an area 1 cm. in diameter on the volar surface of the forearm. Seventeen hours later there was a mild pruritus, and redness of the skin over an area slightly larger than that exposed. The reaction in this experiment was much more mild than those in Experiments 1 and 7.

7. Phenylhydrazin hydrochlorid (1 part) plus sodium bicarbonate (2 parts) was applied over an area 1 cm. in diameter on the skin of the volar surface of the forearm. Pruritus and redness appeared within three and a half hours. The course was similar to that in Experiment 1, the skin returning to a normal appearance in four days.

8. Pure phenylhydrazin base (98 per cent) fluid was rubbed with cotton over an area of skin 1 cm. in diameter. No evidence of hypersensitivity was noted.

9. This experiment was repeated rubbing the solution in with sand to scarify the skin. Again there was no evidence of hypersensitivity.

10. Following some of the reactions above described, the mixture of bismuth subcarbonate, zinc oxide, zinc stearate, glycerin, and carbon detergent was used locally. At other times, it was not used. No difference was noted in the subsidence of symptoms.

**Conclusions.** 1. A case of skin hypersensitivity to phenylhydrazin hydrochlorid is herein presented.

2. The reaction manifests itself in the form of pruritus, swelling, vesicle formation, pain, and desquamation locally and in surrounding areas—never thus far as a generalized reaction.

3. The skin reactions were much more prompt in appearance, and more severe when the phenylhydrazin hydrochlorid was mixed with two parts of sodium acetate or sodium bicarbonate thus rendering the reaction markedly alkaline.

4. The application of phenyl, sodium acetate, hydrochloric acid, pure hydrazin hydrochlorid and pure phenylhydrazin base in fluid form to the skin, with and without excoriation, by means of sand, failed to produce any evidence of hypersensitivity.

5. The patient is not hypersensitive to any of the fractions of the compound phenylhydrazin hydrochlorid but only to the compound as a whole and these reactions can be accentuated by the addition of certain alkalies not in themselves responsible for the reactions.

6. Medications locally applied did not appear to influence the course of the reactions.

NOTE.—We wish to thank Dr. John A. Killian and Dr. Stanley R. Benedict for their kind aid and advice during this study.

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## FURTHER STUDIES IN THE DIETARY CORRECTION OF OBESITY.

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IN the treatment of obesity, it is necessary to appreciate the fundamental facts of the metabolism of the obese and to adapt the generally accepted principles of dietetics to meet the needs of this physiologic anomaly. Unfortunately, many of the basic facts are not well established. The dietetic study of obesity here reported, an elaboration of those already published (see this Journal, 1929, 177. 339), has been carried out in an effort to examine some of these points.

The excess weight in obesity represents chiefly fatty tissue, composed for the most part of fat and water. Stored water may be removed from the body by several channels; insensible perspiration, sweat, feces and urine. In the light of present knowledge, however, the sole mechanism for the removal of fat is by the natural process of combustion which follows upon the mobilization of the stored material by a reversal of the storage process. As the rate of fat deposition is controlled by the excess of food intake over the body needs, the rate of lysis and combustion of fat is governed by the excess of energy output over intake. The rate of weight loss is, therefore, influenced by variations in both intake and output. The two factors are interdependent, the output being very definitely

influenced by the intake. In the treatment of obesity, the attention must then be focused neither upon the intake nor upon the output but upon the difference between the two. The goal is not a low intake *per se* nor a high output but rather the lowest intake at which can be preserved so high an output that the maximum possible difference between intake and output is secured. Starvation, even though not contraindicated for other reasons, does not meet the situation because it produces such a depression in basal and total metabolism that we by no means approach this maximum difference.

In establishing the essential components of the diet, the protein requirements demand careful consideration. The studies on undernutrition of many investigators, among whom may be mentioned Benedict,[1] Lusk,[2] suggest that the deficiency of nitrogenous food with its consequent negative nitrogen balance is one of the principal factors associated with the concomitant depression of metabolism. There must be in the diet, therefore, enough protein to maintain nitrogen balance and prevent this starvation depression of metabolic level. It must also be remembered that, as Woodyatt[3] and others have indicated, a transformation of protein into available glucose in the body can occur in times of carbohydrate stress. Finally, in the construction of any diet of a restrictive type, the biologic value of the proteins employed becomes important. The evaluation of these principles is not a simple matter. Arbitrarily, therefore, a standard of 1 gm. protein per kilo of ideal weight was adopted for the present study, the protein being selected only from sources with the highest biologic values.

The amount of carbohydrate is one of the radical changes in the present diet as compared with that previously described.[4] The earliest teaching, dealing with carbohydrate metabolism, employed the apparent principle that the combustion of fat and glucose are interdependent in a definite numerical ratio. The evidence also seems to show that fat is not available as a source of glucose.[5] Furthermore, the work of Woodyatt,[3] Shaffer[6] and others has taught us to recognize antiketogenic factors other than the carbohydrate of the diet and to deal with the glucose equivalents. Evidence which is now accumulating from various sources questions a fixed ratio for the combustion of glucose and fat molecules. These conceptions have influenced us to abandon the method previously employed of supplying carbohydrate in an amount which maintains a theoretical ketogenic-antiketogenic ratio of 1½ to 1. The first diet used in this series of cases called for no carbohydrate whatever for the purpose of known carbohydrate metabolism. Later diets contained carbohydrate up to a total of 20 gm. in order to obtain a desired effect upon the nitrogen balance.

The fat in the molecular mixture which the body burns is derived almost entirely from the body stores.

If the metabolic factors above presented were the sole considerations, the diet would contain protein requirements with only the inseparable carbohydrate and fat. The vitamin content of the food must, however, be kept in mind. Weight was given to the reasonable assumption that human fat compares favorably with other animal fat in its capacity to store the fat-soluble vitamins. Accordingly, our patients received definite amounts of actively growing yeast, orange juice and whole milk. These amounts were small but materially increased the carbohydrate and fat values of the diet.

An adequate salt supply must be given. Quantitative data on this subject are not too reliable, but the preference is to err on the side of an excess rather than a deficiency. Kalak water contains most of the necessary cations and anions. It is also alkaline, a factor which was considered at the outset as of importance in dealing with potential acidosis. More recently, we have used with good results, Tyrode's solution without glucose.

A diet constructed on the basis of the protein, vitamin and salt requirements made possible an average daily intake of less than 360 calories. It was thought this diet would provide the lowest possible intake consistent with the maintenance of a normal basal metabolic rate and normal daily activities with their concomittant extra demand for energy expenditure. Thus, the maximum difference between intake and output would be obtained and the most rapid loss of weight, without injury to the organism, result.

The menu, which was used principally at the outset, was composed of fresh meat and egg white. Approximately 100 gm. of lean steak was the backbone of each of the two largest meals. When necessary, fresh fish was given at intervals. Egg white was employed to balance the daily protein requirement. This was perhaps more desirable than the meat in view of the presence of fat and protein in almost equivalent amounts in even lean meat. On alternate days, the patient received either 100 cc. of whole milk or 100 cc. of orange juice and 50 cc. of actively growing yeast. One glass of Kalak water was given three times a day. The later diets contained carbohydrate sufficient to make a total of about 20 gm. This increment was supplied in the form of 5 per cent vegetables.

The question of how much water should be ingested daily has not been definitely answered as yet. We asked the patient to drink at least 2500 cc. a day. At times, the daily intake reached 4500 to 5000 cc., due to the enthusiasm of the patients.

This report deals with 13 patients who were dieted in the hospital under the especially rigid conditions of the metabolic service. At the inception of the dieting period, the average weight of the patients was 259 pounds (maximum, 427; minimum, 180). The average duration of the diet was fifty-nine days. The average final weight was 224 pounds. The average weight loss was 35 pounds in fifty-nine days (maximum, 104 pounds in one hundred and seventy-

TABLE I.

| Case No. | Age. | Initial weight, lbs. | Preliminary diet. | | | Restricted diet. | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Calories. | Duration days. | Weight loss, lbs. | Weight at outset, lbs. | Duration days. | Final weight, lbs. | Weight loss, lbs. | Calories. | Protein, gms. | Carbohydrate, gms. | Fat, gms. |
| 9026 | 60 | 359 | 3690 | 4 | 5 | 354 | 178 | 268 | 86 | 328 | 53 | 17 | 7 |
| 9567 | 58 | 432 | 2260 | 5 | 5 | 427 | 176 | 323 | 104 | 358 | 65 | 14 | 5 |
| 9601 | 33 | 195 | 2870 | 4 | 0 | 195 | 45 | 166 | 29 | 353 | 58 | 12 | 8 |
| 2379 | 24 | 220 | .. | .. | .. | 218 | 47 | 194 | 24 | 310 | 46 | 14 | 8 |
| 4140 | 39 | 275 | 2850 | 6 | 3 | 272 | 25 | 256 | 16 | 319 | 55 | 11 | 7 |
| 1223 | 27 | 234 | 2630 | 2 | 0 | 234 | 14 | 217 | 17 | 337 | 60 | 9 | 7 |
| 4242 | 35 | 181 | 2900 | 2 | 1 | 180 | 13 | 171 | 9 | 303 | 50 | 10 | 7 |
| 753 | 50 | 207 | 1450 | 5 | 4 | 203 | 8 | 198 | 5 | 375 | 62 | 18 | 7 |
| 10,007 | 43 | 191 | .. | .. | .. | 191 | 14 | 178 | 13 | 353 | 59 | 12 | 7 |
| 8127 | 45 | 248 | .. | .. | .. | 248 | 51 | 227 | 21 | 395 | 63 | 17 | 9 |
| 8890 | 39 | 240 | .. | .. | .. | 240 | 47 | 210 | 30 | 457 | 70 | 21 | 10 |
| 8511 | 52 | 228 | .. | .. | .. | 228 | 50 | 203 | 25 | 369 | 63 | 10 | 9 |
| 7466 | 39 | 378 | 1868 | 7 | 1 | 377 | 97 | 305 | 72 | 382 | 56 | 21 | 8 |
| Average | 42 | 261 | 2570 | 4 | 2 | 259 | 59 | 224 | 35 | 357 | 58 | 14 | 8 |

six days; minimum, 5 pounds in eight days). The average rate of weight loss was, therefore, slightly less than 0.6 of a pound per day.

The average figures for the diet provided were 58 gm. of protein, 14 gm. of carbohydrate and 8 gm. of fat—a total of 360 calories. Attention should be called to the fact that nearly two-thirds of the total exogenous calories were protein. These figures represented the food supplied but by no means indicated the mixture actually metabolized. This must include the body substance, chiefly fatty tissue and protein tissue, which was burned.

The loss of protein tissue may be estimated from a study of the relative intakes and outputs of nitrogen during the dieting period. The nitrogen balance of several of these patients has been carefully determined and constitutes the subject of a separate report.[7] Briefly, the evidence at hand indicates that during the first three weeks of rigid dieting, patients may lose nitrogen to the extent of 40 to 50 per cent above the nitrogen intake. The addition of 10 to 15 gm. of carbohydrate to the diet causes an abrupt drop in the nitrogen output and the attainment of a permanent nitrogen balance without the alteration of the nitrogen intake. On the most recent patients, an attempt was made to prevent the preliminary loss of nitrogen by adding this carbohydrate to the initial diet. We have so far been unable to prevent this early loss but have strikingly reduced the duration of the loss period to two weeks.

It is, therefore, obvious that protein tissue was lost to some extent by all of these patients. There can, however, be no question that fatty tissue was the greatly predominant source of weight loss. In the absence of data regarding the exact nitrogen loss on several of these patients, we have omitted this protein tissue loss from the calculation of the approximate average metabolic mixture which the body actually handled.

The average food intake, as recorded above, was 58 gm. of protein, 14 gm. of carbohydrate and 8 gm. of fat. If we assume that the body weight loss was fatty tissue containing 14 per cent water, the observed weight loss, 0.60 pounds or 270 gm., is equivalent to 232 gm. of dry fat. The body actually handled, therefore, approximately 58 gm. of protein, 14 gm. of carbohydrate but 240 gm. of fat. The glucose equivalent was 72, most of which came from protein and less than $\frac{1}{5}$ from carbohydrate in the diet. The carbohydrate intake was accordingly no index of the antiketogenic properties of the metabolic mixture. The ketogenic-antiketogenic ratio was 3.4—certainly a high ratio and still there was no evidence of clinical acidosis. A further support of this method of calculating the metabolic mixture is obtained by noting that the total daily calories of this mixture was 2520, which differs but slightly from the average caloric value of the selected diet on admission.

It is noteworthy that of a total daily energy exchange of approximately 2500 calories, only 360, or one-seventh of the total, was sup-

plied as food. The remaining six-sevenths came from the energy reserves. For weeks these patients maintained health and mental and physical vigor on an intake of less than 3 calories per kilo per day. Two patients whose weights at the beginning of the restricted diet were 354 and 427 pounds respectively, took less than 2 calories per kilo per day for six months.

It is necessary to emphasize the fact which has been reported by many that although the patient may burn 250 gm. of her stored fat per day she does not necessarily lose weight every day. The curve of the daily weight change is a series of ups and downs with frequent periods of no apparent weight change. As has been repeatedly demonstrated, these irregularities are intimately associated with the storage and release of relatively large quantities of water. The influence of this phenomena on the true weight loss is minimized if the period of observation is sufficiently long. It is possible to predict with gratifying precision the weight to be expected from the deficiency in exogenous calories.

Drugs and endocrine preparations were not used. Any preparations of value must remove fat by hastening its combustion by increasing the metabolic level. Thyroid is contraindicated because the basal metabolism of the obese is already 20 to 50 per cent above the ideal level.[8] The various ovarian and panhormonic preparations have no demonstrable influence on the metabolic rate.[9]

The clinical side of the picture is encouraging. In spite of the early negative nitrogen balance, these patients were apparently not starved physiologically. The personal efficiency was greatly increased. All varieties of minor aches and pains disappeared. There were no observed complications attributable to the diet. The opinion that there is no primary deficiency in the diet rests upon the careful observations of the two patients who for six months carried on the diet under close observation in the metabolic pavilion.

The contraindications to this dietary régime seem to be chiefly the lack of courage of the physician. It has, however, not yet been used on patients who were not in residence in the hospital and who were not primarily problems in obesity.

For some time we have been intrigued by the statements of fat people that they eat little or nothing and yet do not lose weight. An attempt has been made to evaluate these impressions by having each new patient eat for three or four days what she ordinarily ate at home. The intakes were carefully weighed. Eight of the patients considered here averaged 2570 calories a day for four days (maximum, 3690; minimum, 1450). But what is more significant, they lost weight, averaging 2 pounds per person, in four days on this intake. In view of a weight loss on this intake, one wonders what must have been the intake at home on which the patient gained weight.

The question is frequently raised as to the permanence of the

weight losses obtained. We believe that no person will gain weight if his energy intake does not exceed his output. The hope for permanence of the reduced weights, therefore, depends upon the development of entirely new dietary habits in the individuals during their periods of strict observation.

In the absence of convincing evidence pointing to a metabolic economy in the obese, one is forced to the opinion that fat deposits result solely from an excess of energy intake over energy output. Conversely, the only method available for the dissipation of this extraordinarily efficient energy reserve is its combustion in the usual manner. The rate at which this combustion can occur is determined by the difference between the caloric intake and caloric output.

The diet described is designed to supply the smallest possible intake while still preserving the maximum output. It consists of sufficient protein to maintain the body requirements plus enough vitamins and salts to prevent the occurrence of the complications which result from deficiencies. The only carbohydrate and fat given are those which are required by the protein and inseparable from accessory food substances. This made possible diets containing but 360 calories per day.

By the use of this diet on 13 patients, a uniformly satisfactory loss of 0.6 pound per day for fifty-nine days was secured. Despite an early negative nitrogen balance, lasting for some weeks, no untoward reactions were observed even after six months rigid adherence to the régime. Although 0.6 of a pound a day seems a very small amount to a patient who has been advised to lose 50 or 100 pounds, any method which will consistently remove four pounds a week and at the same time actually increase the vitality and sense of well being of the subject is worthy of careful investigation.

**Summary.** 1. A reduction diet is described which supplies only the body requirements of protein, vitamins and salts.

2. The diet averages 360 calories per day which are derived from 58 gm. of protein, 14 gm. of carbohydrate and 8 gm. of fat.

3. Thirteen patients showed an average weight loss of 0.6 of a pound per day for fifty-nine days.

4. Clinically, the patients were greatly benefited and showed no untoward reactions in spite of: (1) an early nitrogen loss; (2) a theoretical ketogenic-antiketogenic ratio of 3 to 4.

5. Patients have been maintained on this rigid diet without complications for six months.

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# BRONCHOLITHS.*

## With Report of Four Cases.

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Since the time of Aristotle calcareous material expelled from the lower respiratory tract has attracted attention. The expectorated material has received many designations, for example, pneumolith, pulmolith, lung calculus or stone, broncholith, bronchial calculus or stone. Apparently in most instances they refer to the same thing. The term broncholith should, perhaps, apply only to those calculi arising from a deposit of calcium salts in the bronchus, for example, in a pocketed bronchiectasis or those arising from a sequestrum of bronchial cartilage acting as a matrix. However, as most authors have used the term broncholith, I have chosen this as the title, in spite of the fact that the majority of bronchial or pulmonary calculi have their origin in the lung tissue outside the bronchus proper.

Paulalion,[1] in his thesis before the Paris Academy in 1891, gives a full discussion of the condition and has been much referred to in the recent literature on the subject.

Wells[2] shows the close analogy between calcification and ossification. His opinion, which is concurred in by Harbitz,[3] is that the processes differ only morphologically, the calcium deposit in calculi being at first in granular form but that it later may become homogeneous through fusion. Wells states "That within such deposits there are usually no living cells and no further change takes place unless it be absorption or the addition of more calcium salts." Whereas, in normal ossification the homogeneous calcium deposits

* Read before the American Climatological and Clinical Association, May 4, 1929.

are closely related to the living cells which not only determine the form of the deposits, but are also able to dissolve the insoluble salts and to cause their deposition as may be needed.

Chemically, with few exceptions, these pathologic deposits have been found quite the same as that of normal bone, 85 to 90 per cent calcium phosphate and 10 to 15 per cent calcium carbonate. Wells quotes Poscharissky as having examined calcified nodules from the lungs of 28 persons and finding bone in 17 (60 per cent). Osler[4] mentions osseous calcification as arising from the bronchial cartilages following prolonged suppuration, as in bronchiectasis or pulmonary tuberculosis; from old pleurisies; from the walls of abscesses; in sclerosis and in true osteotomata and very rarely in tracheobronchial mucous membrane, the seat of old disease.

In another article Wells[5] discusses metastatic calcification accompanying destructive bone diseases, for example, osteomalacia, bone tumors, either primary or secondary and leukemic conditions. In these diseases there is rapid liberation of calcium salts into the blood stream and, as quoted by Harbitz,[3] Virchow showed, in 1885, that certain organs and tissues are predisposed to calcareous infiltration, namely, the lungs, the endocardium of the left ventricle, the pulmonary veins, the gastrointestinal mucous membrane and the kidneys. Calcium salts, according to Wells,[5] are absorbed to a greater amount than can be held in solution by the arterial blood, so that no calcium is found deposited in the right side of the heart, but after the blood has passed through the lungs and lost a large part of its carbon dioxid, the calcium salts are precipitated in the pulmonary veins, the left heart and taken up by adjacent tissues. Watt,[6] concurs with the theory of Wells,[5] that it is probably loss in the carbon dioxid content of the blood which permits the precipitation of the calcium salts in the tissues. There has been no cellular action demonstrated which can be responsible for the deposition of the salts. He further points out that calcium deposits in tissues have no organic structural framework nor is there any fibrous tissue capsule surrounding them.

The deposition of calcium salts in the bronchopulmonary lymph nodes is probably a process of filtration alone. (Bloor.[7])

Tuberculosis has been regarded as the disease in which broncholiths are most apt to arise. Flint,[8] in reporting 2 cases, says, "The histories are consistent with the doctrine which holds pulmonary calculi to be obsolete tubercles," and many authors since are of the same opinion.

Jackson[9] divides lung stones into three classes: "(1) True calculi; (2) calcium deposits in tissues that sloughed loose and gained entrance into the bronchus; (3) pneumoconiotic, silicotic or anthracotic material that has loosened by disintegration or suppurative liquefaction of the encasing tissues."

In the routine study of lungs by Roentgen ray one is struck by

the frequency with which calcareous deposits are seen in the pleura and in the lung structure, particularly in the region of the hilum and in an advanced tuberculous process of long duration. However, the occurrence of inflammatory reaction leading to ulceration into a bronchus is a relatively rare occurrence if one is to judge by the number of cases reported in the literature. Just why calcified masses should in most instances remain silent throughout life and in a very small per cent become freed and expelled, is not known.

Samuel West,[10] in speaking of the frequency of broncholiths, says he knows of only one set of figures dealing with this phase of the subject which gives the incidence as 16 in 1000 cases of tuberculosis. He adds that he thinks this an unusually high percentage. He gives a list of 15 cases which he found recorded in 1902, each reported by a different observer.

In a review of the English language literature since 1900 I have found 18 cases reported. Of this number, two authors, Pritchard[11] and Lyter,[12] report 2 cases each, the others reported a single case, Jackson[9] (apparently this same case is reported[13]), Pratten,[14] Benjamin and Mollison,[15] Friedman,[16] Maytum,[17] Vinson,[18] Shasted,[19] Cole,[20] Stivelman,[21] Fox,[22] Elliott.[23] Of these 18 cases, 7 occurred in tuberculous patients and 8 in apparently nontuberculous.

Jackson,[24] in his book on bronchoscopy, says: "Broncholiths have been found and removed bronchoscopically in a number of instances at the Bronchoscopic Clinic," but he does not state the incidence, merely mentioning 3 specific cases, which are included above.

Pritchard[11] encountered 2 instances of broncholiths among 7000 patients studied at Battle Creek Sanatorium.

Stivelman[21] reports only 1 such occurrence in "5000 cases of tuberculosis personally observed." Curiously enough, the 4 cases I have to report were seen in the past six years. The incidence seems above normal, as the number of cases seen by me in the past eighteen years could hardly exceed 5000, both tuberculous and nontuberculous.

The stones vary in size from granular particles as described by Jackson[24] to that reported by Fredault,[10] weighing 139 gr.

They are usually grayish-white in color, gritty and hard, but sometimes are putty-like in consistency. They are usually rough in outline and when multiple may be faceted.

The calculi may be single or there may be a large number expectorated from time to time. Boerhaave's[4] case of Sebastinus Vaillantius, the famous botanist, who expectorated 400 calculi before he died of "phthisis calculosa," and Flint's[8] case of a farmer who expectorated more than a pill box full and who, thirteen years later, was in good health, and the case reported by Portal,[10] who expectorated 500 stones, seem to have been the most prolific. One of Pritchard's[11] cases expectorated 40 to 50 calculi during four days.

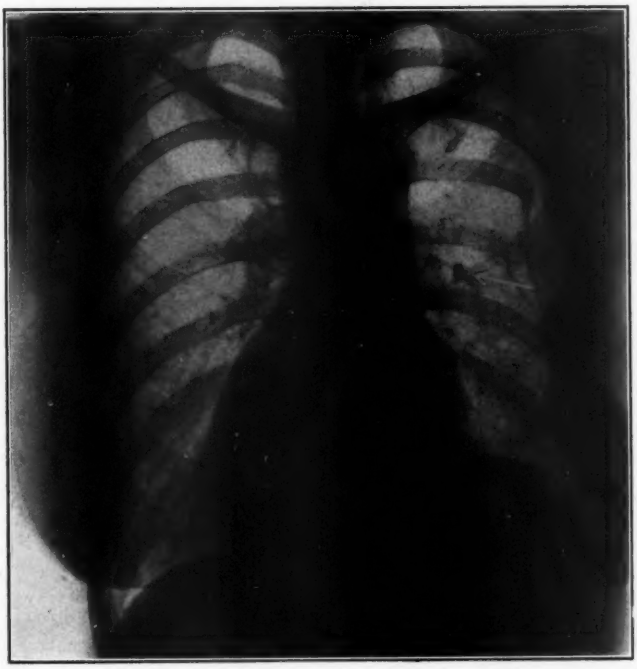

FIG. 1.—Case III. At the end of the white arrow, in the right hilum region, is seen a small calcified mass.

FIG. 2.—Same patient as in Fig. 1, four months later, showing disappearance of calcification at end of arrow.

FIG. 3.—Photograph of broncholith expectorated by Case III. Magnified 5 times.

FIG. 4.—Case IV. Lipiodol shows normal bronchial tree in the right middle lobe and the descending trunks of the left. At the end of the arrow, above the right hilum, is seen a large calcified area.

FIG. 5.—Same patient as in Fig. 4. At the end of the arrow is seen an area of pneumonitis in film taken five days after expectoration of broncholith.

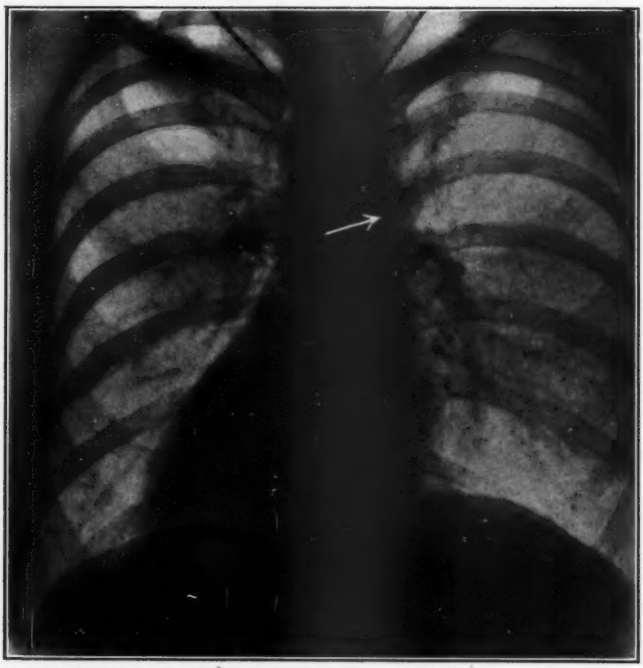

FIG. 6.—Same patient as in Figs. 4 and 5, one month later. Shows pneumonitis having cleared and the area of calcification disappeared entirely.

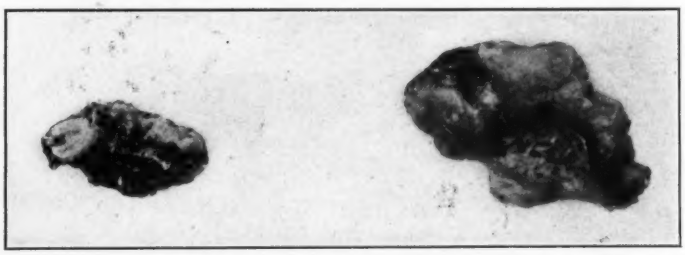

FIG. 7.—Two broncholiths expectorated by Case IV. Magnified 3¼ times.

The symptoms of broncholithiasis vary with the size and shape of the stone from an unconscious raising of the stone with sputum, when the hard substance is discovered in the mouth; to the very severe "stone asthma" or bronchial colic, in which there may be felt intense pain beneath the sternum accompanied by a sensation of impending suffocation.

The expulsion of the stone, however, is usually preceded and accompanied by a severe paroxysmal cough and frequently is accompanied by streaked sputum or hemoptysis.

Elevation of temperature, malaise and prostration may be present preceding the expulsion, but in most instances recorded the symptoms were largely relieved shortly after the stone was expectorated.

In several cases reported the paroxysmal cough preceded the expulsion of the stone by several weeks and the bronchoscopic removal of broncholiths in cases of bronchopulmonary suppuration by Jackson[9, 24] and Vinson[18] emphasize the serious results consequent upon the retention of calculi in the bronchi—bronchiectasis, lung abscess or empyema.

In tuberculosis as well, one wonders if there may not be an infrequent connection between the posthemorrhagic pneumonia or a pneumonic spread and a possible retained broncholith.

Two of the 4 cases reported below occurred in advanced tuberculosis. Cases III and IV are unusual in the fact that the calcareous deposit was plainly visible in an Roentgen ray film before the broncholith was expelled and had disappeared in subsequent film. Jackson[13] reports 1 similar case.

**Case Reports.** CASE I.—P. Y., male, aged thirty-six years, a traveling salesman, died on November 7, 1925, of advanced tuberculosis, having been ill with tuberculosis seven years prior to death. He developed a large cavitation in the upper lobe of both lungs and spat up four to five cupsful of sputum daily. During the last two years of life he expectorated many small calculi without symptoms. Their nature was discovered when the hard substances reached the mouth. Other larger ones were accompanied by considerable bronchial colic and when this occurred the sputum was always blood tinged. None of these calculi were preserved, but several, from ½ to ¾ cm. in diameter, were seen by the author.

CASE II.—Mrs. J. M., aged thirty-one years, married, was seen on December 8, 1921, with acute pleurisy and a moderately advanced lesion in the upper left lobe. She went to a health resort in 1922, where she remained until December, 1929, and returned home. She expectorated 1 small stone in 1919, then none until the fall of 1924, when she raised 1, more or less circular in shape and 1 cm. in diameter, and daily the next three weeks raised smaller ones, 2 or 3 a day, and again in the fall of 1925 raised 1, 1½ cm. in diameter, followed by 6 or 8 smaller ones in the next three or four days. In 1929 she raised 1 on March 11 and 1 on March 12, both about ½ cm. in diameter. She has never had bronchial colic, but the sputum is frequently blood tinged. The stones are not always accompanied by streaks, but are usually embedded in heavy, mucopurulent sputum. She expelled, all told, from 50 to 60 stones.

None of these stones were preserved. The disease has progressed and she now has extensive involvement in both lungs with cavitation.

No history of stone spitting was obtained until the specific question was asked, "Have you ever raised any stones?"

CASE III.—E. A. S., female, aged fifty-two years, single, a teacher, has had the following disorders: In 1915 her right breast was removed for nonmalignant tumor; left ovariotomy and appendectomy in 1920; in 1923 tonsillectomy; iritis off and on since 1922. In October, 1925, lobar pneumonia followed by interlobar empyema with operation, October, 1925. Recovery was slow. She has had many negative sputa examinations. The urine is normal. In August, 1928, during a violent coughing attack, she raised a small stone followed by a small quantity of foul-tasting sputum. This was followed by a rather severe bilateral bronchitis, which continued until the latter part of October. No more stones were expelled and since that time she has been in excellent health.

In this case a film taken, October 2, 1928 (Fig. 4), showed the disappearance of a calcified area which was noticed in film of June 14, 1928 (Fig. 3).

The calculus was saved and is shown in Fig. 5. It is ½ cm. in diameter, hard and very rough.

CASE IV.—F. V., female, aged fifty-four years, single, a teacher, was first seen on April 8, 1926. Her father died at the age of thirty-seven years of rapid tuberculosis, when the patient was two and a half years of age. Her mother died at the age of seventy-five years from a heart attack.

At the age of nineteen years the patient had an acute nephritis and was ill for about a year; also an operation for gastric ulcer in 1916; tonsillectomy in 1918. In 1922 she had an attack of grippe and was in bed three weeks and away from work six weeks. Following this attack she continued to cough, raising a cupful of thick, yellow sputum daily, which was negative for tubercle bacilli. There were many râles in the right middle lobe, with feeble breathing. Lipiodol injected showed normal bronchial trunks. Left antrum was found to be filled with pus and was cleared by irrigation. Following this, cough disappeared and she was perfectly well from August 1, 1926, to July 1927. On July 15, 1927, she had general malaise, a temperature of 100° to 101° F. and began coughing. The temperature continued elevated and the cough persisted in paroxysms, until, on July 20, during a violent coughing attack, she raised two pieces of calcified material in thick, yellow, blood-tinged sputum. Cough continued for about a month, when it again disappeared. A Roentgen ray made (Fig. 7), July 20, 1927, showed an area of cloudiness above the right hilum and the disappearance of a calcified mass which was noticed in previous films. In a film made, August 13, 1927 (Fig. 8), the area of pneumonitis had disappeared and she has had no further attacks. The two calculi were preserved and are shown in Fig. 9. One was 1 cm. in diameter, the other ¼ by ½ cm., both very hard and irregular and each faceted.

**Summary and Conclusions.** 1. The occurrence of broncholiths was known and reported by the oldest medical observers. The stones probably originate most frequently in an obsolete tuberculosis of a bronchopulmonary lymph node in or near the hilum.

2. In a fairly thorough review of the literature in the English language since 1900, 18 cases were found in addition to the 15 cases found by West in 1902—4 more cases are added in this paper, making a total of 37.

3. The condition probably is more frequent than reported cases would lead one to suppose as the expectoration of stones may be easily overlooked in history-taking, for example, Case II reported above.

4. The erosion of a calculus into a bronchus may produce serious results should the stone remain in the bronchus. Perhaps such an occurrence may occasionally account for a posthemorrhagic spread in tuberculosis as well as producing a bronchiectasis, lung abscess or empyema.

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## ALLEGED MENSTRUAL FEVER IN PULMONARY TUBERCULOSIS.

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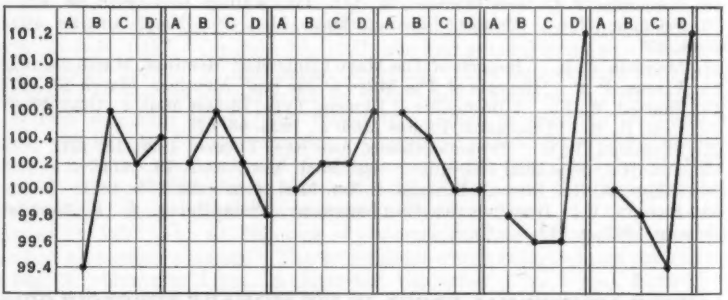
Elevations of temperature in tuberculous females are claimed to have a cyclic association with menstruation. It is maintained that such cyclic fever can be identified as a characteristic entity so as to have a diagnostic and prognostic significance.[1,2] Premen-

strual, menstrual, postmenstrual and intermenstrual fever have been described.[3,4,5,6] Kessel,[7] in contrast, observed that in 96 of 100 cases no rise in temperature occurred within five days preceding the onset of the menstrual period. Welch[8] studied 500 cases and observed a depression in temperature during menstruation.

The identity of a characteristic cyclic type of fever in pulmonary tuberculosis is at variance with the irregular course of the temperature observed in the disease. In order to arrive at exact conclusions an examination was made of the temperature charts of 100 tuberculous females, in all stages of the disease, who had been in this institution for six or more months and who had an equal number of normal menstrual cycles. Six months was chosen as a minimum period of observation because, as will be shown later, only by observing patients over at least such an interval can conclusions of a diagnostic value be obtained. For convenience the menstrual cycle was divided into four periods: Premenstrual, seven days before menstruation; menstrual, the actual flow; postmenstrual, seven days after menstruation; intermenstrual, the time between the post and premenstrual periods. The highest temperature during each of these respective periods for six successive months was charted, as shown in the accompanying chart. Such a scheme enables one to perceive not only fever but slight elevations of temperature which might have significance when relatively compared. All temperatures were taken per rectum.




Six consecutive temperature curves with relation to menstruation in the same individual: *A*, premenstrual period, seven days before menstruation; *B*, menstrual period, actual flow; *C*, post menstrual period, seven days after menstruation; *D*, intermenstrual period, time between post- and premenstrual period.

The temperature curves showed no regular changes associated with the menstrual cycle which could be identified as a characteristic entity. It is true that a given patient may have a decided rise of temperature at most premenstrual periods for several consecutive months. From this we could erroneously conclude that this is an

example of premenstrual fever, but this same patient would have similar elevations at various other times during the same month. Likewise, analogous curves with the stress of changes upon the menstrual, postmenstrual and intermenstrual periods were frequently noted. Moreover, very often a patient would have a rise of temperature only at some one period for a few consecutive months, but over an observation of many months this apparent cyclic rise disappeared. Thus in chart the highest temperature for two consecutive months occurred during the menstrual period, yet during the remaining months of her stay at the sanatorium this high temperature was present at various other periods. This emphasizes the necessity of observing a patient for a minimum of six months. Conclusions otherwise would be deceptive.

It is thus easy to observe that tuberculous patients show rises of temperature at some arbitrary time during the month, either at the premenstrual, menstrual, post or intermenstrual period, ignoring the fact that they show similar rises at other intervals even during the same month. To state then that such a rise, because it occurs at that period, is a periodic rise and is diagnostic of tuberculosis is an erroneous conclusion. For a rise of temperature to be cyclic it should occur solely at some one interval and only at that interval over an observation of several months. Dluski[9] found no influence on temperature during menstruation in 56 per cent of 300 tuberculous women examined for several months. In others the temperature proved extremely variable during menstruation even in the same women. There was no special type, and his experience does not indicate that fever during menstruation is necessarily a sign of tuberculosis. Wiese[10] studied the temperature curves of 500 definitely diagnosed tuberculous women under sanatorium treatment. He concludes that there is no type nor regularity of thermic disturbances associated with menstruation.

We were unable to obtain data of a prognostic value from this study. Except in patients who have a marked elevation of temperature over a continued period, it is extremely difficult to make a prognosis in phthisis from an examination of the temperature chart alone, since the prognosis depends on numerous factors other than the temperature.

Assuming that fever associated with menstruation could be identified as an entity in tuberculosis, to have any diagnostic value it should be characteristic of the disease. But even normally physiologic rises of temperature are attributed to menstruation.[11,12] Moreover, in numerous diseases, such as scarlet fever, typhoid fever, rheumatic fever, chlorosis, premenstrual fever has been known to occur.[13,14,15]

**Conclusions.** Though catamenia may be associated with a rise of temperature in tuberculous patients, this phenomenon has no diagnostic or prognostic value because:

1. Fever associated with the menstrual cycle has been noted in normal women and in numerous diseases other than pulmonary tuberculosis.

2. It cannot be identified as a characteristic entity in tuberculous individuals since fever occurs at different periods with relation to menstruation in different tuberculous females, or even in the same patient if examined over a properly long period.

3. A diagnosis and, except in characteristic instances, a prognosis in pulmonary tuberculosis cannot be made from an examination of the temperature curve alone.

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# REVIEWS.

ROENTGENOGRAPHIC TECHNIQUE. By DARMON ARTELLE RHINEHART, A.M., M.D. 388 pages; 159 illustrations. Philadelphia: Lea & Febiger, 1930. Price, $5.50

THE author of this textbook has covered his problem admirably. The book contains 20 chapters dealing with electricity and electric current, Roentgen ray machines, dark-room equipment and technique, and basic roentgenographic technique with various experiments to illustrate the value of such technique. He illustrates the position that will demonstrate the parts to best advantage. The author not only gave the value of his own experience in this book but he has covered the literature fairly well in order that one may be able to have a comprehensive idea of what other men are doing in the examination of various parts. This book affords one a comprehensive outline in discussion of the entire roentgenographic technique and should be of great value to anyone doing this type of work. The publisher is to be congratulated on the illustrations and the print.

E. P.

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THE DIETARY OF HEALTH AND DISEASE. By GERTRUDE I. THOMAS. Pp. 276; 3 illustrations. Second edition. Philadelphia: Lea & Febiger, 1930. Price, $2.50.

THE purpose of the book is to serve as a basis for the study of diet in health and disease in schools of Nursing and departments of Home Economics. The consideration of food in its relation to the body needs and the processes by which the body makes use of food are treated in a concise yet comprehensive manner so that the background for the study of foods is adequate.

Diet in relation to the treatment of disease is recognized by the author and the information is up to date, special emphasis being placed on the influence of pregnancy on the teeth, recent developments in diabetic feeding, ketogenic diets and liver therapy for anemia.

The outline for the laboratory course in practical dietetics and suggestions to instructors are of value.

Classification of hospital diets and methods of calculating the caloric value of diets are scientifically treated.

An adequate textbook for nurses.

F. C.

PRACTICAL HANDBOOK FOR DIABETIC PATIENTS. By ABRAHAM RUDY, M.D. Pp. 180; 15 illustrations. Boston: M. Barrows & Co., 1929. Price, $2.00.

THIS volume is written for the laity. The author devotes several chapters to a description of diabetes, its complications and treatment, emphasizing particularly those facts that the patient should know. The greater portion of the book is devoted to diets, recipes and food values. There are 180 recipes, many of which are from numerous nationalities, so modified that they may be taken by diabetic patients. Apparently the author had in mind particularly the care of the Jewish and other immigrants. These recipes are indexed at the end of the book. The Reviewer feels that the author has presented a book that should be of unusual value to the physician, dietitian and patient.

L. J.

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THE TREATMENT OF VARICOSE VEINS. By T. HENRY TREVES-BARBER, M.D., B.Sc. Pp. 120; 11 illustrations.

THE author presents the subject matter in great detail, emphasizing the detail with repetition. He is apparently very well informed on all phases of the condition, but makes no reference to experimental or statistical proofs of his statements and theories. The description of the technique of treatment is comprehensive, but leaves some doubt how to proceed after the first injection.

The injection treatment does not remove the pathology and introduces a chemical irritant which will always produce inflammation. Such treatment is far more out of date than so-called old-fashioned operative method which removes the pathology.

E. E.

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ANNALS OF THE PICKETT-THOMSON RESEARCH LABORATORY. VOL. V. The Pathogenic Streptococci, Their Rôle in Human and Animal Disease, Continued. By DAVID THOMSON, O.B.E., M.B., CH.B. (EDIN.), D.P.H. (CAMB.), and ROBERT THOMSON, M.B., CH.B. (EDIN.). Pp. 392; 46 plates. Baltimore: The Williams & Wilkins Company, 1929.

VOLUME V of these Annals includes three monographs on the pathogenic streptococci as followed:

VIII. The Rôle of the Streptococci in Oral and Dental Sepsis.

IX. The Rôle of the Streptococci in Tonsillitis and Pharyngitis.

X. The Rôle of the Streptococci in Puerperal Sepsis and Septic Abortion.

These three monographs contain over 1100 references to literature and they are illustrated with 46 full-page plates of photographs of colonies and stained smears of streptococci. The photographs show rather conclusively that the appearance of the colonies on Crowe's medium is one of the most important means we have of differentiating between the large numbers of varieties of streptococci.

This volume, along with Volumes III and IV, is very thoroughly indexed. With Volumes VI and VII (to be published) they will represent an encyclopedia of information on the streptococci and the part they play in human and animal diseases. They cannot fail to be of great service to the future research worker in that they will present the present state of human knowledge on the subject, and they will, therefore, form the basis of further researches and advances for years to come. Those annals impress upon us very emphatically that the streptococcus group is very much larger and more complicated than was ever imagined, and all future researches on this group will require to be carried with much more precision and care than they have been done in the past. W. K.

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DIE MEDIZIN DER GEGENWART IN SELBSTDARSTELLUNGEN. Pp. 219. Leipzig: Felix Meiner, 1929. Price, 8.50 Mk.

SEVEN years ago the Leipzig publishing house of Felix Meiner began the publication of small volumes, each containing several autobiographies of men prominent in their line of work. This has now reached the point that in eight fields of human endeavor 30 volumes have been published, including 197 (mostly German) contributors. Though in many cases the most prominent are noticeable by their absence, nevertheless such a project must constitute a source of reference of great value and increasingly so as the series progresses. Following a portrait and short description of the author's birth, education and previous record, the major space is devoted to his scientific aims and achievements that not only give insight into his own personality but also into the thought of the period and specialty. E. K.

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PETTIBONE'S PHYSIOLOGICAL CHEMISTRY. By J. F. MCCLENDON, PH.D. Fourth edition. Pp. 368; 17 illustrations. St. Louis: The C. V. Mosby Company, 1929. Price, $3.75.

THIS revision of a textbook of Physiological Chemistry which has already been in use a number of years will no doubt meet the approval of those desiring a text which presupposes only a moderate amount of chemical training. The book covers the field of phy-

siological chemistry in adequate fashion although comparatively little space is devoted to fundamental chemical considerations, thus making it much too brief to be used as the sole source of information in a medical school course in physiological chemistry. This is particularly to be noted in the chapters on proteins and carbohydrates where very little attention is paid to even the composition of amino acids and simple sugars. More modern physical methods such as hydrogen-ion determinations find little or no mention in the experimental part of the book. The experiments are otherwise adequate. J. A.

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JAMES MACKENZIE INSTITUTE FOR CLINICAL RESEARCH. GASTROINTESTINAL DISEASES. Edited by DAVID WATERSTON, M.A., M.D., F.R.C.S. (EDIN.). Pp. 278; 13 illustrations. New York: Oxford University Press, American Branch, 1929. Price, $3.25.

THIS publication differs from the previous ones of the James MacKenzie Institute for Clinical Research in that it is not a report of work done there, but a presentation of a series of eleven lectures delivered at St. Andrew's by prominent British physicians and surgeons, all but one from elsewhere. The subjects touch upon the physiology, the pathology and the clinical aspects of gastrointestinal disease. Several statistical reports are included but the number of cases referred to are small. Few if any new data are included, but the accepted British viewpoint about many interesting clinical problems is clearly and entertainingly presented. T. M.

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THE VOLUME OF THE BLOOD AND PLASMA. By LEONARD G. ROWNTREE, M.D., and GEORGE E. BROWN, M.D. Pp. 219; 17 illustrations. Philadelphia: W. B. Saunders Company, 1929. Price, $3.00.

IN observations on the cellular concentration of the blood, both in clinical medicine and experimental conditions, and on possibly related disturbances in other organs, it is obvious that accurate knowledge of the total blood volume would be highly desirable. This booklet presents the results of the considerable experience of the authors with a dye method which they feel is nontoxic, reliable and has furnished valuable information not only in such conditions as plethora and anemia, but in the relation of blood volume to hypertension, cardiac hypertrophy, etc. Criticisms of the limitations of this and other methods are frankly discussed and details for the proper performance of the test given. We are inclined to agree that the dye method is the best available and may furnish valuable data, but also believe that it unavoidably leaves a number of factors uncontrolled. E. K.

MANUAL OF DETERMINATIVE BACTERIOLOGY. By DAVID H. BERGEY. Third Edition. Pp. 589. Baltimore: The Williams & Wilkins Company, 1930. Price, $6.00.

THE elaborate system of classification of the bacteria into families, tribes and genera by a committee on characterization and classification of the Society of American Bacteriologists has made it very desirable to be able to place in the hands of students a more detailed key for the identification of species than any that was available up to a decade ago. This need was in a measure supplied by the first edition of Bergey's Manual in 1923 and is more adequately supplied by the third edition (1930).

More than 200 additional organisms are included in the revision. Two new tribes of soil bacteria have been recognized, each containing a single species. Genus Eberthella has been divided by separating the dysentery group from the typhoid group, the former group being placed in the genus Shigella while the latter group is retained as genus Eberthella. Four additional genera have been recognized in family Mycobacteriaceæ, each genus representing characteristic groups of soil bacteria.

The greater number of newly-described bacteria fall in genera Flavobacterium, Pseudomonas, Phytomonas, Lactobacillus and Bacillus. These additions have necessitated the reconstruction of the keys for these genera. Another change in the Manual is an attempt to arrange the genera of tribe Bacterieæ in a way which appears to be more logical. A new key for this tribe as well as the transposing of the locations of the genera in the tribe is presented.

The manual should stimulate efforts to perfect the classification of bacteria as well as prove a valuable aid to the student of bacteriology. W. K.

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# BOOKS RECEIVED.

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## NEW BOOKS.

*Plant Biology.* By H. GODWIN, M.A., PH.D. Pp. 265; 67 illustrations. Cambridge: University Press, 1930. Price, 8s. 6d.

*The Harvey Lectures, Series 24, 1928–1929.** Pp. 216; 36 illustrations. Baltimore: The Williams & Wilkins Company, 1930.

*The Surgical Clinics of North America, Vol. X, No. I, February, 1930, Mayo Clinic Number.* Pp. 174; 82 illustrations. Philadelphia: W. B. Saunders Company, 1930.

* Reviews of titles followed by an asterisk will appear in a later number.

*The Volume of the Blood and Plasma.*† By LEONARD G. ROWNTREE, M.D., and GEORGE E. BROWN, M.D. Pp. 219; 17 illustrations. Philadelphia: W. B. Saunders Company, 1929. Price, $3.00.

*Progressive Medicine, Vol. I, March, 1930.* Edited by HOBART AMORY HARE, M.D., LL.D. Pp. 328; 23 illustrations. Philadelphia: Lea & Febiger, 1930.

*The Growth of the Mind.* By SIR ROBERT ARMSTRONG-JONES, C.B.E., M.D., D.Sc., F.R.C.P., D.L. Pp. 29; 13 illustrations. Edinburgh: Oliver & Boyd, 1929. Price, Sixpence.

*The Bacteriophage and Its Clinical Applications.** By F. D'HERELLE, Professor of Bacteriology. Pp. 254. Springfield, Ill: Charles C. Thomas, 1930. Price, $4.00.

*Surgical Diagnosis, Vol. I.** Edited by EVARTS AMBROSE GRAHAM, A.B., M.D. Pp. 919; 508 illustrations. Philadelphia: W. B. Saunders Company, 1930. Price, $35.00, set of 3 volumes.

*Surgical Diagnosis, Vol. II.** Edited by EVARTS AMBROSE GRAHAM, A.B., M.D. Pp. 871; 834 illustrations. Philadelphia: W. B. Saunders Company, 1930. Price, $35.00, set of 3 volumes.

*Tonsil Surgery.** By ROBERT H. FOWLER, M.D. Pp. 288; 103 illustrations. Philadelphia: F. A. Davis Company, 1930. Price, $10.00.

*Peptic Ulcer.** By JACOB BUCKSTEIN, M.D. Vol. X of *Annals of Roentgenology.* Edited by James T. Case, M.D. Pp. 337; 287 illustrations. New York: Paul B. Hoeber, Inc., 1930. Price, $12.00.

*Cours de Chimie Biologique, Vol. II, Partie Speciale.* By PIERRE THOMAS. Pp. 393; 12 illustrations. Paris: University Press of France, 1929. Price, 60 francs.

*A Syllabus of Lectures on Obstetrics for Nurses.* Prepared by a Committee appointed by the American Gynecological Society. Pp. 38. Copies may be obtained from the Chairman of the Committee, 23 E. 93d St., New York City. Price, 50 cents.

## NEW EDITIONS.

*A Textbook of Psychiatry.* By D. K. HENDERSON, M.D. (EDIN.), F.R.F.P.S. (GLAS.), and R. D. GILLESPIE, M.D. (GLAS.), M.R.C.P., D.P.M. (LOND.). Pp. 526. Second edition. New York: Oxford University Press, 1930. Price, $5.50.

*Practical Psychology and Psychiatry.* By C. B. BURR, M.D. Pp. 378. Sixth edition. Philadelphia: F. A. Davis Company, 1930. Price, $2.75.

*Medical Treatment of Disease.* By ROBERT DAWSON RUDOLF, C.B.E., M.D. (EDIN.), F.R.C.P. Pp. 516. Third edition. Canada: The University of Toronto Press, 1930. Price, $4.00.

*Applied Physiology.* By SAMSON WRIGHT, M.D., M.R.C.P. Pp. 552; 128 illustrations. Third edition. New York: Oxford University Press, 1929. Price, $5.50.

* Reviews of titles followed by an asterisk will appear in a later number.
† See p. 706 this number.

# PROGRESS
OF
# MEDICAL SCIENCE

## MEDICINE

UNDER THE CHARGE OF

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AND

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**The Race and Sex Distribution of the Lesions of Syphilis in 10,000 Cases.**—Without enumerating all of the statistical findings in this study by TURNER (*Bull. Johns Hopkins Hosp.*, 1930, **46**, 159), it is of interest to note in these 10,000 ambulatory patients a few of the following facts: Clinically recognizable syphilitic affections of the cardiovascular system occurred in 10 per cent of all the cases and the proportion of males to females and negroes to whites was approximately as 2 is to 1. Uncomplicated aortitis with or without aneurysm occurred much more frequently in males than in females and in negroes than in whites. Aortic regurgitation is more than twice as common in males as in females and is just about as common in whites as in the negro. Syphilitic angina pectoris was rare and was seen more frequently in whites than in negroes. Central nervous system syphilis was observed in late syphilis in 39.3 per cent of white males and only 15.9 per cent of colored males. The ratio was approximately the same among the females of the two races, but the nervous system involvement was only about one-half as frequent as with the males. General paresis was very much more frequent in the whites than in the blacks and the same thing applies to tabes dorsalis. Cerebral vascular syphilis was more common in the negro than in the white. Syphilitic stricture of the rectum was confined almost entirely to colored females. Pulmonary tuberculosis among the negro syphilitics was decidedly less than in the general negro population and diabetes was no more frequent among the syphilitics than among the nonsyphilitics.

**Studies on the Effect of Nitroglycerin, Amyl Nitrite and Acetylcholine on Hypertension.**—ZEISS and BRAMS (*Am. Heart J.*, 1930, **5**, 300) write that the medical treatment of hypertension is frequently unsatisfactory

and often most disappointing, possibly due to the fact of the traditional belief that nitrites reduce blood pressure regardless of the cause. They decided to reinvestigate the influence of these drugs on account of the very many contradictory reports that now occur in the literature. They summarize their investigations as follows: Nitroglycerin produces a fall in blood pressure in normal controls, but inconstantly in patients with hypertension. Amyl nitrite causes a fall in both controls and hypertensive cases. A secondary rise above the previous level of the pressure occurs in a certain number of cases of patients who receive amyl nitrite or nitroglycerin. Amyl nitrite exerted its effects more markedly and lasted almost as long as did the effects obtained by nitroglycerin, but disagreeable symptoms frequently followed the use of this drug. Acetylcholine was found to be inert in both the controls and the cases of hypertension, a finding quite different from the claims made for this drug in literature.

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**Brucella Abortus Infection in Man.**—The increasingly large number of Brucella infections reported throughout the country have focused interest on the Brucella group of organisms. There has been a tendency among clinicians to consider various types of organisms belonging to the group of Brucella (Alkaligenes) as being capable of producing very much the same clinical symptoms in all cases. GIORDANO and SENSENICH (*J. Lab. and Clin. Med.*, 1930, **15**, 421) have analyzed a series of 35 cases and have come to the conclusion that Brucella abortus infection in man runs a clinical course somewhat at variance to that of Brucella melitensis infection. In this series of 35 cases reported by the authors they give the following data: There were 20 men and 15 women in the group and the preponderance of infection is in the second, third and fourth decades. Occupation, they say, is an etiologic factor only in so far as it provides opportunity for infection, such as those engaged in the handling of infected animals. Consequently there is a very much greater incidence among farmers and farmers' wives than in any other occupation. The disease is commoner in rural communities because raw milk is more generally used. This is probably an important mode of infection, as judged by reports from others, of the disease occurring in individuals who have ingested milk from abortus-infested cows. The onset is usually insidious, with fatigue, low fever, headache and joint pains. Often there is involvement of the upper respiratory tract. The disease may be characterized by either an acute or chronic course, the latter corresponding closely to the type of disease observed in an individual who has undulant fever of the melitensis type. In Brucella abortus infection acute types are more frequent than the chronic and this the authors consider to be an important differential point between the two forms of Brucella infection. They divide the cases into several groups, such as the septic, the arthritic, neurologic, visceral and glandular, according to the predominance of the symptoms. Fever is the most constantly present symptom and, of course, is invariably present. There is some tendency to undulation when the temperature charts are studied, but the period of undulation is shorter than in Brucella melitensis infection. The whole febrile course is shorter. Arthralgia, arthritis and neuritis are other rela-

tively common symptoms which deserve to be accentuated. The blood count shows that the white cells are decreased in number, as a rule, so that late in the course of the disease the count varies from 6000 to 10,000. Only two blood cultures were positive in twenty attempts. The agglutination reaction is the most valuable clinical laboratory evidence of the disease. A positive reaction occurs early and the agglutinin titer is high. There seems to be no relationship between the titer of the agglutinins and the severity of the disease. Rest in bed seems to be the important symptomatic treatment.

## SURGERY

UNDER THE CHARGE OF

T. TURNER THOMAS, M.D.,

PHILADELPHIA, PA.

**Distribution of Blood in Shock.**—Blalock and Bradburn (*Arch. Surg.*, 1930, **20**, 26) clain that the oxygen content of blood from the right side of the heart, portal vein, femoral vein, external jugular vein, the renal vein and the femoral artery has been determined in dogs to which barbitol had been given for varying intervals of time. Similar studies were made after a low blood pressure had been produced by hemorrhage, the injection of of histamin, trauma to the intestinal tract, trauma to the cerebrum and trauma to one of the posterior extremities. In the control experiments, the oxygen content of blood from the right side of the heart and that of blood from the portal vein were approximately the same; that of blood from the femoral vein was usually lower and that of blood from the external jugular vein slightly higher. The oxygen content of blood from the renal vein was usually definitely higher than that of the mixed venous blood. Approximately the same relationship existed between the values of the oxygen content of blood from the various sites after a low blood pressure had been produced by hemorrhage, by histamin and by trauma to the brain. The oxygen content of blood from the portal vein was much higher relatively after trauma to the intestines, while that of blood from the extremities and head was low. The oxygen content of blood from the femoral vein of a traumatized leg was high, while that of blood from the opposite extremity and head was low. The oxygen content of blood from the renal vein was relatively high in all the experiments. These observations suggest a local accumulation of blood at the site of trauma to a large area, such as the intestinal tract or an extremity, and are evidence against the action of a histamin-like substance that produces a general bodily effect.

**Primary Intramuscular Hemangiomas of Striated Muscle.**—Davis and Kitlowski (*Arch. Surg.*, 1930, **20**, 39) say that primary angiomas of striated muscles are no longer rare tumors, as is indicated by the 212 cases here collected. It is a slow-growing tumor, congenital in origin,

with trauma playing a rôle more in its growth than in its origin. It occurs about equally in both sexes. The age of onset is before the twenty-first year in the great majority of cases, the largest number occurring before the eleventh year. The tumor may occur in any striated muscle. The lower extremities are most commonly affected and the upper extremities are next. The larger and more powerful muscles are involved most frequently. The size of these tumors range from that of a nut to that of a small pumpkin. The chief symptoms are pain, swelling and functional impairment. The tumor may be compressible and change in size with changes of posture. It is usually soft, but may be hard, smooth or lobulated, movable or fixed, circumscribed or diffuse. The diagnosis is difficult. Aspiration of normal blood is a valuable aid. The existence of simple angiomas is questioned and the cavernous type is considered the only one found in striated muscle. On section it has the characteristic appearance of a blood-filled sponge. Microscopically the typical picture is that of blood-filled spaces containing normal blood, which either are lined by endothelium or have walls composed of fibrous connective tissue. The muscle fibers show degeneration ranging from hyaline to fat replacement. The only treatment of value is excision, while the prognosis is excellent.

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**Primary Carcinoma of the Ureter.**—Rousselot and Lamon (*Surg., Gynec., and Obst.*, 1930, **50**, 17) declares that primary carcinoma of the ureter is a rare lesion. Previous to the case reported here only 49 cases have been recorded in the literature. The most common type of carcinoma is the so-called papillary epithelioma. Less frequent is the squamous-cell tumor, of which the present case is an example. Ureteral carcinomata metastasize widely, traveling by venous and lymphatic channels. Renal calculi are occasionally associated with this neoplasm. Many authors believe that stones, by their irritative action, are an important causative factor in the production of epithelial tumors of the genitourinary tract. In the cases here reviewed, no frequent association of stones and tumor could be discovered. The two most contant symptoms of this disease are pain and hematuria. The condition is rarely diagnosed before operation or necropsy. Roentgen ray and cystoscopic examinations are the most important diagnostic aids. Removal of the affected ureter and kidney is the treatment of choice. The course of the disease following any form of treatment has been discouraging. In only one recorded case was the patient symptom-free two and a half years after being first observed.

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**Some Surgical Problems in Jaundiced Patients.**—Smith (*Am. J. Surg.*, 1929, **7**, 799) claim that the fear of operating unnecessarily on a patient in the cancer age, with possible catarrhal jaundice, need not delay surgical intervention after careful study of the case. In obstructive jaundice, due to malignancy in this series, pain, occasionally severe, was found in more than half the cases. It was relatively more common in duct than pancreatic carcinoma. Silent stone in cases of jaundice thought to be due to malignant disease is disappointingly uncommon, but is a reason for exploration. Biliary intestinal anastomosis in malignant obstruction of the ducts is a palliative measure, which seems worth while. An occasional case thought at operation to be carcinoma of the pancreas, will turn out to be pancreatitis.

# THERAPEUTICS

UNDER THE CHARGE OF

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AND

SOMA WEISS, M.D.,

ASSISTANT PROFESSOR OF MEDICINE, HARVARD MEDICAL SCHOOL, BOSTON, MASS.

**Some Pharmacologic Aspects of Tribromethylalcohol ("Avertin").**—In discussing the relative value of the rectal administration of anesthetics, PARSONS (*Brit. Med. J.*, 1929, p. 709) claims that the advantage of this channel of administration is that it is more comfortable for the patient, it does not require an anesthetist and it is specially convenient for operations about the head and neck. The disadvantages are the risk of irritation to the mucosa, the difficulty of maintaining a constant concentration in the tissues and the impossibility of controlling its action after administration. Avertin is a trade name for tribromethylalcohol, which has received widespread use as an anesthetic in Europe. On the basis of pharmacologic observations, Parsons claims that special care must be exercised in the preparation of solutions of avertin for anesthesia. Heat over 50° C., light and air are apt to produce decomposition products irritant to the rectal mucosa. Tribromethylalcohol in doses just sufficient to induce deep anesthesia exerts no appreciable effect upon the cardiovascular system. When administered in larger amount it slows the cardiac rate and weakens the force of the beat. Under experimental conditions the coronary vessels dilate and the blood pressure falls. Tribromethylalcohol anesthesia is accompanied by marked slowing of respiration, which is due at least partly to diminution of voluntary movements and to absence of reflex activity from the respiratory tract. Certain peculiarities of the respiration may be observed when the anesthesia is deep. Respiratory paralysis is the cause of death from toxic doses. Tribromethylalcohol is excreted in the urine over a period of several days; but more than 50 per cent is excreted in the first twenty-four hours. The chemical nature of the elimination cannot be determined at present. It is suggestive that the elimination occurs in the form of an organic compound of bromin.

**The Clinical Use of Tribromethylalcohol ("Avertin") Narcosis.**—EDWARDS (*Brit. Med. J.*, 1929, p. 713) states that the variations in depth of anesthesia produced by similar doses of avertin on different patients is so great that one cannot set out definitely to produce anesthesia solely by this method. Once a patient is narcotized with avertin, only a very small quantity of inhalation anesthetic is required to com-

plete the anesthesia. The falling asleep is gradual and peaceful. Even if the narcosis has been slight, there will be no memory of anything from the time of injection. The events of the next twenty-four or thirty-six hours will not be remembered with any clearness. It is of particular value in highly nervous patients, with cases of Graves' disease. The drug is contraindicated in patients with inflammatory and ulcerated conditions of the rectum and colon; in cases with severe renal and hepatic lesions, acidosis, advanced cachexia and serious blood diseases. There is a fall of 10 to 30 mm. of mercury in the blood pressure during this narcosis. The breathing is shallow and the rate normal or slightly slow. Variable degrees of cyanosis may be present. It takes twenty to thirty minutes to reach completion of the anesthesia. The preliminary measures are an enema the night before operation, repeated the next morning if necessary. One-tenth gram per kilo of body weight is a safe dose. Untoward reactions almost always are due to overlarge doses. The weighed powder of tribromethylalcohol may be dissolved slowly in water at 38° C. It is provided in a concentrated solution with amylene hydrate—1 gram in 1 cc. The approximate amount of the solution is measured out and distilled water to make 2.5 to 3 per cent solution is added at 38° C. The mixture is shaken until clear solution results. *The temperature must never exceed* 40° C. Just before administration a drop of 1 in 1000 Congo red solution is added to 5 cc. of the dilute solution. The color of the solution should remain bright orange red. The solution is injected into the rectum slowly through a catheter and funnel. The injection should take three to four minutes. It is best to give the rectal injection thirty minutes before the expected start of the operation. Ether, chloroform or local anesthetics are used to supplement tribromethylalcohol. Combined with volatile or local anesthetics, avertin is a satisfactory anesthetic agent. It should be remembered, however, that it is not controllable and cannot safely be used as the sole anesthetic agent. It requires an experienced anesthetist to control the superimposed anesthesia. In certain cases and types of patients avertin is of great value. As a routine agent it is hardly practicable.

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**Use of the Duodenal Tube in the Treatment of Infestation by Tænia.** —Margulis (*München. med. Wchnschr.*, 1929, **76**, 1510) strongly recommends the administration of tæniacids by means of the duodenal tube on the basis of an extensive experience of the past two years. Although this method of administration is exceedingly satisfactory in adults, it is exceptionally so in children. Not only does the method seem to diminish the danger of intoxication on account of the more rapid action and elimination of the anthelmintic agents employed, but, owing to this fact, larger doses of these drugs may be given with safety as absorption is diminished. As a result, the method yields a higher proportion of effective cures than does oral administration. The usual preliminary period of starvation and cleaning out of the gastrointestinal tract by laxatives precedes the administration by duodenal tube just as it does the oral administration or vermifuges.

# PEDIATRICS

UNDER THE CHARGE OF

THOMPSON S. WESTCOTT, M.D., AND ALVIN E. SIEGEL, M.D.,

OF PHILADELPHIA.

**The Incidence of Sinusitis in Asthmatic Children.**—CHOBOT (*Am. J. Dis. Child.*, 1930, **39**, 257) states that the incidence of sinus infection in asthmatic and also in normal children is much higher than has heretofore been believed. In his series of 100 asthmatic children, 60 were boys and 40 were girls. Fourteen had their first attack in the first year of life and 19 in the second year. These figures compare closely with reports of other observers. Fifteen of these patients had negative skin reactions. The incidence of the age of onset is parallel to that in hypersensitive patients. Fifteen per cent of the sensitive patients had their first attack in the first year and 23 per cent in the second year. The 15 negative cases in this series were studied and a positive family history was obtained in 5 children. Forty-one of the entire series both sensitive and nonsensitive had sinus infections as demonstrated by Roentgen ray examinations. Chobot recommends conservative treatment but he feels that puncture and irrigation should be performed when conservative measures have failed.

**Citric Acid Milk in Infant Feeding.**—GONCE and TEMPLETON (*Am. J. Dis. Child.*, 1930, **39**, 265) made a comprehensive study of the feeding of citric acid milk to infants. One of there chief claims for its use is that it is easy to prepare. They found that the hydrogen-ion concentration of the gastric contents at the height of digestion in infants who were fed on whole citric acid milk averaged 3.72 in the normal infants, 4.15 in the abnormal infant. The gastric curves at the height of digestion on this type of milk were uniformly small. The average individual curves being less than 1 mm. in diameter and the largest being less than 3 mm. in diameter. Infants seemed to like citric acid milk and in itself it never caused persistent vomiting. It was found that the infant fed on whole citric acid milk both in the hospital and at home gained weight better than with the normal expectancy. The stools of these infants were of a smooth pasty or firm consistency and were somewhat more frequent in number than infants fed on simple milk dilutions. The citric acid in the amount of 4 gm. to a quart of milk did not show any toxic action on the kidneys. The authors feel that since citric acid milk appears to equal lactic acid milk in the beneficial results and because of its constant acceptibility and ease of preparation that it is specially fit for use in rural districts and in all homes in which ice is not avilable.

**The Etiology of Infantile Spasmophilia.**—GERSTENBERGER, HARTMANN, RUSSEL and WILDER (*J. Am. Med. Assn.*, 1930, **94**, 523) present additional data in substantiation of the theory advanced by them in a previous report. This theory is that there are three factors essential

in the development of infantile spasmophilia and these factors are, rickets, exposure of the rachitic infant to the influence of the antirachitic factor in one form or another sufficient to produce partial healing and interruption of the exposure or inadequacy of the exposure. They report the appearance of typical spasmophilia following interrupted therapy in two rachitic infants who were exposed to sunlight and in another rachitic infant who received inadequate therapy in the form of human milk possessing some antirachitic power. The two infants who were exposed daily at noon to the sun for an hour as it passed through glass that was more permeable to ultraviolet rays than is ordinary window glass. The other infant developed spasmophilia after and while being fed milk from a wet-nurse whose arms, face and neck were exposed daily to the summer sun for forty-five minutes. This milk had antirachitic power but not in a marked degree and in this rachitic infant furnished an inadequate intake of the antirachitic factor. Another child developed mild symptoms of spasmophilia after a single erythema-producing exposure to the quartz light. The authors define infantile spasmophilia as a symptom complex occurring principally in spring and fall peaks and characterized by a higher excitability of the nervous system.

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**Poliomyelitis.**—RILEY (*J. Am. Med. Assn.*, 1930, **94**, 550) emphasizes the importance of the early diagnosis before paralysis appears. He feels that when a patient, especially a child, appears prostrated out of proportion to the temperature, with flushed face, anxious expression, mild injection of the throat, rapid pulse, a coarse tremor or movement, the head tilted on the neck, stiffness of the spine and pain on anterior flexion, and an increase in the cellular and globulin contents of the spinal fluid, the diagnosis of poliomyelitis is definite and convalescent serum should be administered. No untoward results from the use of convalescent serum should be feared and even if there is an error of diagnosis no harm will follow from its administration. Early and repeated spinal drainage and the use of convalescent serum are most important in the preparalytic stage of the disease. When it is realized that the pathologic changes of this disease are located in the central nervous system it is obvious that in order to prevent as much as possible the paralysis and to obtain the greatest functional activity. Prolonged rest in the recumbent posture is necessary. As a result of this method of handling the number of patients with poliomyelitis recovering without appreciable paralysis during the 1928 epidemic in Maryland and in recent epidemics elsewhere is most encouraging. Under proper conditions the good recovery was found between 70 and 80 per cent of the cases as compared with 20 per cent in cases receiving less intensive treatment. He feels that under appropriate treatment 90 per cent of the deformities which have followed epidemics may be eliminated and deformities as an after result of the disease should entirely disappear. This statement is based upon the early treatment of the disease as an absolute necessity. Along with the use of human serum, early hospitalization and the guidance of an orthopedic surgeon are additional factors which produce low mortality rate, low average of total paralysis, a striking reduction of paralysis of severe grade and complete prevention of deformities.

**Chorea.**—EPSTEIN (*Arch. Ped.*, 1930, **47**, 119) claims that chorea in children is a cerebrospinal and an autonomic functional neurosis and that it requires some infection, physiologic distress or psychologic insult to convert it into a disease process. The signs and symptoms of chorea are the result of the primary neurosis and secondary process may be pathologic, physiologic or emotional. Where a choreic child may show evidence of pathologic, physiologic and psychologic abnormalities, one of these usually predominates and suggests the proper group diagnosis. Chorea frequently leaves in its wake a damaged heart or an impaired neuropsychic system. Both the choreic process and the secondary disorder contribute to the cardiac or nervous breakdown and treatment should be prophylactic as well as curative. Every effort should be made to keep nervous and emotional children in good physical and mental health. Careful guidance in the home and school life is necessary in order to avoid an overtax. During the acute stage good food, complete rest, hygienic care, salicylates, bromides or hypnotics will be of help in bringing about recovery. Recurrences of chorea must be prevented by proper and constant attention to the well-being of the child, especially as regards the hours of work, rest and play.

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**Measles Prophylaxis with Serum of Adults Who Had Measles in Childhood.**—VAN CLEVE (*Arch. Ped.*, 1930, **47**, 124) believes that immune measles goat serum or antistreptococcus measles antitoxin will be the best form of serum to use because it will be easily available and will be standardized. He feels that convalescent serum is equally as good but not generally practical and there is some danger of transmitting tuberculosis or lues. Serum of adults who had measles in childhood is not as efficacious, but where the others are not to be had it will answer. It will protect the young and malnourished and modify the disease in the older children and lessen the danger of complications in children under four years. The undernourished, the rachitic, the tuberculous and delicate are much safer with full protection with a dosage sufficiently large to assure this. In older children and adults it would seem better to give a dosage sufficient to modify the disease as it had been shown that serum only protects from four to six years while the modified cases have a lasting immunity that is indefinite.

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## DERMATOLOGY AND SYPHILIS

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**Syphilitic Disease of the Pulmonary Arteries.**—HARE and ROSS (*The Lancet*, 1929, ii, 806). The authors report a case of pulmonary arteritis together with a review of 23 previously published cases. Of the

24 cases, 16 had a definite syphilitic basis, 2 were syphilitic but with nonsyphilitic histology, 1 followed typhus and the remaining 5 were primary. Age and history of the patient give the sole clue to the possible luetic origin in those affected. To quote from the author's summary: It is found that syphilis is by far the most important etiologic factor in older patients. Primary noninflammatory sclerosis of unknown etiology is found in younger patients. In the syphilitic cases the lesions in the intrapulmonary arteries take the form of an obliterative arteritis, usually most severe in the smaller branches and arterioles. This condition leads to a raised blood pressure in the lesser circuit. Dilatation and hypertrophy of the main pulmonary artery follows with atheroma of the right and left pulmonary arteries and larger branches, whether the latter show inflammatory lesions or not. The right side of the heart becomes greatly dilated and hypertrophied. Clinically the cases are characterized by dyspnea, cyanosis and hemoptysis, and in the later stages by progressive congestive heart failure with a regular pulse. Syphilitic arteritis of the pulmonary arteries, while admittedly rare, is worthy of notice, since by early diagnosis antisyphilitic treatment might afford some hope of amelioration of the symptoms.

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**Arsphenamin Sensitization Tests Including a Report of Arsenical Dermatitis Due to the Arsenobenzol Radical of Bismarsen (Bismuth Arsphenamin Sulphonat).**—SCHOCH (*Am. J. Syph.*, 1930, **14**, 75). The desirability of determining patients' cutaneous tolerance to the arsphenamins prior to the administration of the drug prompted the author to attempt an evaluation of the different methods of testing for cutaneous hypersensitiveness to the arsphenamin group. The various methods previously employed are discussed, and the functional skin test of Jadassohn (eczema test of Bloch) is selected as the most promising at the present time. It was found that strongly positive reactions were obtained with this method in all patients with known cutaneous hypersensitiveness to the arsphenamins (four), and negative in a series of 96 persons who showed no cutaneous intolerance to the drug. A case of generalized subacute dermatitis with erosive stomatitis following the administration of bismarsen is included. Evidence is given that the patient's hypersensitiveness was acquired, that it was specific for the arsenobenzols, and that it was not due to the bismuth content of bismarsen. The author believes that this is the first case of extensive dermatitis due to the arsenobenzol radical of bismarsen reported in the literature. Passive transference tests by the Prausnitz-Kustner method and by Perutz's modification of the Konigstein-Urbach method gave negative results. A résumé of the literature on arsphenamin hypersensitiveness is included, with special reference to cutaneous methods of testing and passive transference. The author's findings are interpreted in the light of the recent literature on the subject. Schoch concludes that in certain reported cases the interpretation of positive reactions as indicative of successful passive transference were specious. He furthermore points out that in all probability active sensitization was brought about by the introduction (intradermally) of minute amounts of the antigen, instead of the specific antibodies which would produce passive sensitization.

**The Kline Slide Precipitation Test for Syphilis.**—MILLER (*Am. J. Syph.*, 1929, **13**, 583). The author emphasizes that in the evaluation of new tests against older and more standard procedures, clinical findings should determine the basis of the comparison. The author reports on 1813 tests done on 1058 patients and divided between proved cases of syphilis and nonsyphilitic cases. The Kline test was compared with the Kolmer Wassermann and the Kahn precipitation tests. Miller found the Kline microscopic slide precipitation test technically simple and requiring less time and apparatus than either the Kolmer Wassermann or the Kahn tests. In addition the reaction is easier to read than that of the Kahn test and is at least as easy to read as the Kolmer Wassermann reaction. The Kline slide test may be done with anticomplementary and slightly hemolyzed blood. The number of positive reactions given by the Kline slide test was greater than the positives produced in the two comparing tests with the exception that in cases of cutaneous syphilis and neurosyphilis the Kolmer Wassermann gave the higher percentage of positives. The Kline and Kolmer tests appeared equal in the recognition of cardiovascular syphilis. The Kline test showed an earlier positive reaction in primary syphilis than either the Kolmer Wassermann or the Kahn test, and it showed a tendency to slower reversal to negative in cases of primary syphilis under treatment. The Kline slide test, however, gave a higher percentage of false positives than either the Kolmer Wassermann or the Kahn tests.

## GYNECOLOGY AND OBSTETRICS

UNDER THE CHARGE OF

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**Irradiation of Ovarian Cancer.**—Perhaps the most carefully checked results of irradiation of the female pelvic organs are those obtained at Radiumhemmet in Stockholm so that when an opinion issues from such a source it is of value. In a report emanating from this institution, HEYMAN (*Surg., Gynec. and Obst.*, 1930, **50**, 173) recalls that in the gynecological literature the five-year cure by operation alone in radically operable cases of cancer of the ovaries is generally estimated to be about 30 per cent, somewhat higher for unilateral and considerably lower for bilateral tumors. Judging from his results a permanent cure is more often obtained from radical operations when combined with postoperative irradiation since in a series of 32 cases he has had 65.6 per cent of five-year cures. In cases in which it has been impossible to perform a radical operation because of metastases, but in which it was possible to remove the ovarian tumors, remarkable results have often

been obtained by radiologic treatment. In a series of 30 such cases treated at Radiumhemmet there are quite a number of patients who for several years have been kept free from symptoms and able to work, there being 7 who were under observation for over five years. In completely inoperable cases the radiologic treatment is of an exacting nature, but can, if correctly carried out, bring with it a remarkable reduction of the tumor and a marked temporary improvement in the general health of the patient. In some cases the patient can be kept free from discomfort for one or two years. In recent years he has performed a re-laparotomy in those cases in which the tumors have shrunk and become mobile under radiologic treatment. In 3 out of 5 such cases the operation was easily performed. He is of the opinion that no permanent results can be obtained in the treatment of cancer of the ovaries without resort to surgical intervention. On the other hand, it is undoubtedly true that an intimate coördination of radiologic and surgical treatment can improve the results considerably. The removal of the ovarian tumors should always be tried, if the risk involved is not too great. If the risk is too great, then it is better to trust to radiologic treatment. In the surgical treatment he advises not to remove the uterus but to retain it so that it may be used as a means of applying the radium in after-treatment, thus enabling the radium container to be centrally placed in relation to the original site of pathologic change. This should be done without delay after operation.

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**Treatment of Gonorrhea with Living Organisms.**—On a previous occasion we have called attention to the method of treating gonorrhea of the female genital organs by means of the subcutaneous injection of living gonococci. LOESER (*Zentralbl. f. Gynec.*, 1930, **54**, 163) who is the originator of the method is able to report the results he has obtained following 1500 such injections, none of which gave any dangerous complications. Within two to four weeks, during which time 1 to 3 such injections are given, a cure was obtained in 60 to 70 per cent of the cases of gonorrhea of the cervix, adnexa and joints. An even higher rate of cure can be expected if the cervical canal is treated with a silver preparation every other day between the injections. He has found that the treatment is of value only in the closed type of gonorrhea in the chronic stage, so that no results may be looked for in disease of the urethra and lower genitals. In order to make the cervical canal a closed organ an occlusive cap is worn over the cervix between treatments. The gonococcal culture which is used for the injection should be reasonably fresh as the older the culture, the less potent it becomes; even transplanting it does not retain its value as these organisms rapidly lose their strength when they are outside of the human body. For best results a mixed fresh culture of 3 or 4 strains of gonococci should be used. In order to show that he has no fear of such injections, Loeser states that in the beginning of his work he was the first experimental animal as he injected live gonococci under his own skin. The injection causes a small somewhat painful infiltration at the site of the puncture which is followed by an erythema within twenty-four hours but which disappears entirely within three days. The body temperature rises a degree or so and the patients may complain of a slight headache, but in no case has there been a general blood stream infection following the injection.

# OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF

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**Cytologic Examination of the Antrum. Review of Cases to Determine Relationship Between the Cytologic and the Roentgen-ray and Pathologic Observations.**—Aware of the potential difficulties in localizing the particular site of involvement in suspected cases of sinusitis, and having previously called attention to the fact that simple lavage of a sinus is untrustworthy as a diagnostic procedure,[1] SEWALL and HUNNICUTT (*Arch. Otolaryngol.*, 1929, **10**, 1) again offer evidence to show that cytologic examination of fluid recovered from the antrum is a valuable adjunct to the diagnostic armamentarium of maxillary sinus disease. After outlining the technique and discussing at considerable length the pathologic histology of sinusitis, comparative roentgenographic, cytologic and postoperative microscopic findings of eighty-three examinations on 55 persons are tabulated. All of these 55 patients had chronic nasal discharge; and on each occasion the material recovered from the antrum showed one or more types of leukocytes. Of the entire series, roentgenograms showed the antrum to be clear in 13 per cent. The test water was macroscopically clear in 18 per cent of the cases presenting cytologic evidence of sinus infection, and it contained easily overlooked shreds of white mucus in 54 per cent. The authors have made the interesting observation that the antra showing the least evidence of infection (by their method) have been associated with definite disease of the opposite maxillary sinus. Employing essentially the same methods for collection and study of the aspirated fluid from 25 cases of suspected sphenoiditis, TILLOTSON—"Sphenoiditis. Value of Cytologic Studies in Diagnosis." (*Arch. Otolaryngol.*, 1929, **10**, 262)—was able to identify mono- or polymorphonuclear leukocytes in the centrifuged specimens in all save four instances. From his results the author concludes that if one bears in mind the clinical symptoms and utilizes the various physical aids at one's disposal, including cytologic study of the sinus secretion, the diagnosis of sphenoiditis—and its commonly associated condition, posterior ethmoiditis—may be made more easily.

**Traumatic Conditions of the Ear in Workers in an Atmosphere of Compressed Air.**—In the condition known as caisson sickness or disease, the symptoms referable to the auditory apparatus occupy a prominent position. Outstanding among the aural symptoms may be mentioned varying degrees of impaired hearing, a feeling of fullness in the ear, tinnitus, vertigo and autophony. These clinical manifestations have been ascribed by various observers: (1) to the direct action of the compressed air-producing hyperemic and hemorrhagic states in the middle and internal ears or rupture of the tympanic membranes; or (2)

[1] *Vide* Retrospect: AM. JOUR. MED. SCI., 1929, **177**, 296.

to the liberation of nitrogen bubbles in the cochlear and vestibular apparatus. After reviewing the literature and citing two illustrative cases, VAIL (*Arch. Otolaryngol.*, 1929, **10**, 113) reports the results of several experiments on rabbits—so conducted as to simulate working conditions as nearly as possible. Microscopically it was found that in every case the lesion was essentially the same, consisting of a copious hemorrhage into the middle ear and its vestibule. Eustachian tubal blockage did not seem to alter the histologic picture. The structures of the internal ear were not affected to any appreciable degree. The author states that trauma can be inflicted on the middle and internal ears of workers in an atmosphere of compressed air, not only during compression but also during, or after, decompression. In the first group the aural trauma is caused by nonequalization of the pressure within and without the middle ear and transmitted to the internal ear, with resulting stasis and hemorrhage; and the symptoms may be temporary or permanent. In the second group the otitic lesions are due to bubbles of nitrogen-forming emboli or areas of necrosis in the internal ear; and the symptoms usually are permanent. It is suggested that in workers in compressed air, the ears and nasal sinuses should be examined carefully; that persons who have suffered traumatic rupture of the drumheads should undergo recompression only if symptoms of caisson illness appear; and that a survey must be made to decide whether the percentage of deafness is uniformly high in individuals working under compressed air.

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**Chondroma of the Larynx.**—In view of the fact that only 69 cases have been collected from the literature, laryngeal chondroma is a decidedly uncommon tumor. Nevertheless, it is an important one, as shown by the instructive case reported by CLERF (*Arch. Otolaryngol.*, 1929, **10**, 241). In Clerf's patient there had been a history of progressive hoarseness of six months' duration but the only findings consisted of immobility of the left vocal cord and impairment of motility of the right cord. Four and one-half years later, however, a previously unrecognizable cartilaginous tumor had grown to a size sufficient to cause a dyspnea that necessitated tracheotomy and subsequent laryngectomy. A convincing photomicrograph is presented.

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**Nonsurgical Treatment of Chronic Middle Ear Suppuration, Based Upon Twenty-five Years' Experience.**—Following a brief résumé of the various bacteriologic, pathologic and clinical aspects of his subject, BECK (*Ann. Otol., Rhinol. and Laryngol.*, 1929, **38**, 1150) says that "up to quite recently,—I have not been very much encouraged in the local treatment of chronic suppuration" (of the tympanic cavity), "but since then, and particularly in the last six months, I feel much encouraged." He refers especially to a method involving capillary suction from the attic region with subsequent insufflation of boracic acid powder containing iodin. Calot's solution also has been used in lieu of the powder, but with less success. The introduction of water into the aural canal is harmful to chronically discharging ears. Local and general contributory pathologic conditions should be properly managed.

# RADIOLOGY

UNDER THE CHARGE OF

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**Physical Therapy in Infantile Paralysis.**—KEY (*Arch. Phys. Therap., X-Ray, Radium*, 1929, **10**, 385) insists strongly that no form of physical therapy should be used until the tenderness has entirely disappeared from the paralyzed muscles, and the duration of this period varies from a few weeks to several months. This acute stage is followed by a convalescent stage which lasts two or three years. This stage is characterized by a tendency of the paralyzed muscles to recover their tone and power, and this is the period during which physical therapy is especially beneficial. Protection from stretching and overwork, graded exercises and local heat and massage may be accepted as beneficial, and their relative value is in the order mentioned. Protection from stretching is most important and is accomplished by the application of splints of metal, leather, wood, etc. This support should be maintained until the muscle has regained sufficient power to support the part without damage, or until all hope that it will regain such power is abandoned. Voluntary exercises must take the form of carefully supervised muscle training. They should be as simple as possible in order that they may be performed accurately, and light at the beginning. When the muscle is too weak to move the part against gravity the patient can be placed in water. Swimming pools are an important feature of many institutions. Heat to the paralyzed muscles is usually applied in the form of a simple electric baker, but diathermy or moist heat or some other form of dry heat may be used. There is no evidence that any particular type of heat is best. The heat is followed by gentle massage and this by muscle exercise. Key does not advise the use of electricity in its various forms because he does not believe that it is of practical value and may do more harm than good because it is apt to divert the treatment from muscle training which is of the utmost importance. This objection is true of light therapy and heliotherapy. Ultraviolet light and heliotherapy may be used for their general effect on the patient, but are not to be regarded as agents for the restoration of paralyzed muscles.

**X-ray Examination of the Heart in Beriberi.**—For some time KEEFER and HSIEH (*Radiology*, 1929, **13**, 211) of Peking Union Medical College have been interested in the cardiac changes observed in beriberi. They have found that in all cases of beriberi with cardiac insufficiency the heart was enlarged, and frequently there was considerable enlargement in cases without insufficiency. The enlargement was principally right-

sided, involving both the right auricle and ventricle, and the pulmonary artery was prominent in many cases. There was also enlargement of the superior vena cava. The size and configuration of the heart changed completely following treatment, and it assumed a normal size and shape after a varying length of time.

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**Activated Ergosterol in Radiation Sickness.**—For the prevention and alleviation of radiation sickness the administration of calcium lactate has proved beneficial. It occurred to SMITH (*Am. J. Roent. and Rad. Therap.*, 1929, **22**, 317) that to increase the body calcium the administration of ergosterol might be more efficient, and it was tried in 55 cases. The product used was a solution of ergosterol in peanut oil and was given in doses of 4 to 8 minims, twice or three times daily, beginning preferably twelve to twenty-four hours prior to treatment and discontinuing twelve to twenty-four hours after irradiation. Seventeen patients who had previously been nauseated by irradiation experienced no nausea after taking ergosterol; 29 patients not previously irradiated had no nausea; 10 patients experienced nausea despite the treatment. Marked relief of all symptoms, except possibly diarrhea, is usually effected. Used as a prophylactic ergosterol prevents all symptoms to a marked degree. Many of the patients experience an unusual sense of well-being an increased appetite. The action is probably effected through the calcium phosphorus metabolism. There is some evidence that the final effect may be brought about through prevention or reduction of hyperirritability of the vagus. The method is apparently applicable both to radium and roentgen treatment.

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**Physical Therapy in Thoracic Surgery.**—Heliotherapy is used routinely by BETTMAN (*Arch. Phys. Therap., X-ray, Radium*, 1929, **10**, 444) during the convalescence of cases of empyema, lung abscess, tuberculosis of the lungs, and bronchiectasis. It is never given until the patient has become afebrile. It is stopped the moment any inflammatory recrudescence occurs. It is started in small doses and gradually increased. It is given for its general tonic effect. In one type of operation, that of cautery lobectomy, it is used for the mild local stimulating effect, granulation of the wound apparently being improved by daily exposures to the quartz lamp. In many unilateral diseases of the lungs and pleura there is a marked tendency to the development of scoliosis. Exercises to overcome deformity should be started as soon as the patient's condition permits. This applies also after plastic operations in empyema and pulmonary tuberculosis. Surgical diathermy is the method of choice for local recurrences following amputation of the breast for cancer, and for tumors of the ribs, chest wall and pleura in which a massive sharp resection and subsequent closure are impossible. For incision of pulmonary tissue the endothermic knife is greatly to be preferred over sharp dissection in that it severs tissue without pressure. The consistency of the lung is such that it is extremely difficult to cut unless it is held taut either by adhesions or by forceps, and so forth. The pressure required, even when a very sharp knife is used, is often sufficient to tear the lung at the point of adhesion or fixation with forceps.

# NEUROLOGY AND PSYCHIATRY

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**Nervous and Mental Phenomena Accompanying Insulin Therapy.**—SEVRINGHAUS (*Arch. Neurol. and Psychiat.*, 1929, **22**, 746) calls attention to the widespread effect and varying symptomatology of hyperinsulinism ranging from effects on the vegetative nervous system such as vasomotor disturbances (due largely, he believes, to stimulation of the adrenal glands), through sensory phenomena and motor disturbances such as hemiplegias, paraplegias, tremor and even convulsions, to mental phenomena such as restlessness, coma, loss of inhibitions, emotional disturbances, hallucinations, amnesia, aphasia, peculiar confusional states, catatonia and negativism. He cites one case of hyperinsulinism which was mistaken in a hospital for alcoholism. He finds that there is nothing specific about the picture except the circumstances under which it is induced, but that in a given patient it tends to run more or less true to type, hence he believes that when a patient knows how hyperinsulinism affects him he is more or less true to type, hence he believes that when a patient knows how hyperinsulinism affects him he is more or less protected. "The variability of sequences in persons is not more surprising than the variability in response to any other stimulus capable of as wide an effect as hypoglycemia can have. The only conditions to be compared with it are carbon monoxid poisoning or any other type of anoxemia, alcoholic intoxication, thyrotoxicosis, cerebral vascular accidents, epilepsy, uremia and dementia, particularly of the catatonic type. These are the conditions with which reactions to insulin are apt to be confused. In diagnosis of coma without a history, the possibility of a coma due to hypoglycemia must be considered. If an analysis of the blood cannot be secured at once, it should be remembered that the therapeutic trial of dextrose given intravenously is never dangerous and may be saving. . . . A single dose of sugar will never cause a diabetic person to develop coma. It should be used without hesitation when hypoglycemia reactions occur."

**Hyperpyrexia Produced by Baths.**—MEHRTENS and POUPPIRT (*Arch. Neurol. and Psychiat.*, 1929, **22**, 700) report on the experimental production of febrile temperatures by the use of continuous baths. The technique of producing hyperpyrexia was, briefly, as follows: Patient was immersed in bath at 110° F. and the temperature of the bath was maintained until the temperature of the patient reached a point within 1½ degrees of the fever desired. Then the temperature of the bath water was gradually reduced until it corresponded with the temperature of the patient. Ordinarily the bath lasted one hour but it was possible to maintain the patient's fever for another hour by wrapping him in

blankets and placing a few hot-water bottles in the bed. "Liquids may be administered by mouth but they must be hot." The baths were administered, as a rule, once a day, occasionally twice a day and at time every other day or every third day. Following the baths the patients felt fatigued but many were able to walk to their rooms. There was a loss of 3 to 5 pounds which was regained by the next morning. (Most of the patients had gained in weight at the end of a series of 14 baths.) There was a regular increase in the pulse. The blood pressure usually fell with an average reduction of 50 mm. systolic and 20 mm. diastolic, with the pressure rising to its former level in twenty-four hours. In rare instances there was an increased systolic pressure. Basal metabolic rate increased from 80 to 100 per cent. Hemoglobin and red cell count tended to show increases with an increase in reticulocytes from 2 to 3 per cent. They noted the following psychologic reactions: In baths at temperature between 98° and 102° the patients were calm and coöpertive; between 102° and 103° they frequently showed signs of restlessness and anxiety; from 103° to 105° they were quieter and rather apathetic; and between 105° and 107° mild confusion frequently occurred lasting in unusual cases for an hour after the patient's return to bed. Following a series of baths there was a frequent diminution of the Wassermann reaction in the cases with syphilis and the paretic types of gold curve tended to change to the tabetic types. These serologic changes usually came on rapidly, frequently within a month of completion of the series of baths. They found that the permeability quotient of the meninges was lowered in all cases when the temperature was greater than 103° F. and continued for at least thirty minutes and repeated on at least five successive days. With 11 paretics, 2 recovered sufficiently to return to work, 4 showed marked clinical improvement, 3 showed slight improvement and 2 were unimproved. Psychometric ratings did not demonstrate improvement after treatment even in the patients able to return to work. The spinal fluid serology was improved in 6 cases. With 20 tabetics every patient was improved in some way and this was particularly true of the "burnt-out" cases showing no positive changes in the spinal fluid. Lightning pains, gastric crises and Charcot joints yielded to hot baths more readily than any other therapy they had previously used. Nine cases of encephalitis did not show generally favorable results. Tremor, spasticity and ocular crises tended to be modified. Relapses after treatment was discontinued were common. Three cases of combined sclerosis showed transitory improvement. A miscellaneous group of patients complaining of pain were markedly improved by the baths. Amyotrophic lateral sclerosis showed no improvement. Excited, psychotic patients tended to have a sedative effect from the baths which were generally followed by restful sleep. The authors conclude that in treating syphilis the malaria therapy is simpler, requires less coöperation on the part of the patient and may have valuable factors in the toxemia produced apart from the fever. On the other hand fever produced by baths is under perfect control, can be maintained at any degree for any length of time up to two hours, may be applied at any time or at any interval, and may be continued daily for at least six weeks, while the patient still gains in weight and maintains his strength. They do not interfere with antisyphilitic therapy of other types and tend to intensify the therapeutic effect of antisyphilitic medication.

# PATHOLOGY AND BACTERIOLOGY

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**The Pathologic Anatomy in Twenty-eight Cases of Addison's Disease.**—Cases of Addison's disease have been reported as the result of a variety of lesions of the suprarenal body. BARKER (*Arch. Path.*, 1929. **8**, 432) presents autopsy data from 28 cases of Addison's disease. Among these, bilateral tuberculosis of the suprarenal glands was found in 25 cases, and advanced bilateral suprarenal atrophy in 3 cases. Acid-fast bacilli were demonstrated in 11 of the 25 tuberculous cases. In all the cases but one, some suprarenal tissue remained, the maximum amount being estimated at 10 per cent of normal. Seventy-three cases are also presented in which there were suprarenal lesions but in which there was no clinical evidence of Addison's disease. In these cases the estimated amount of suprarenal tissue remaining was never less than 10 per cent of normal. In only 10 cases was more than 75 per cent of the tissue apparently destroyed.

**Experiments to Determine Whether There is a Filtrable Form of the Tubercle Bacillus.**—The very conflicting evidence regarding the existence of a filtrable form of the Bacillus tuberculosis prompted GLOYNE, GLOVER and GRIFFITH (*J. Path and Bact.*, 1929, **32**, 775) to make a careful study of the problem. Filtrates from 26 tuberculous sputa prepared in various ways, produced no tuberculous lesions when injected into 50 guinea pigs. Nine guinea pigs, inoculated with filtrates of uterine, placental, or fetal materials taken from tuberculous women, showed no evidence of tuberculosis. Histologic sections confirmed the macroscopic findings. Complement fixation tests made at the time of death with the blood sera of the guinea pigs were positive in two instances and negative in fourteen. Filtrates prepared from tuberculous lesions in various organs of men, monkeys, rabbits and cattle, representing six human and three bovine viruses, were inoculated into 26 guinea pigs and one rabbit. None of these showed gross or microscopic evidence of tuberculosis when subsequently killed. Cultures of the filtrates used in inoculation remained sterile. Filtrates of avian viruses were tested on three fowls and one rabbit, all of which remained healthy. Tuberculin tests upon the inoculated animals taken just before termination of the experiments were uniformly negative. The occasional occurrence of doubtful lymph gland enlargement at autopsy was tested by the inoculation of 8 guinea pigs, all of which remained free from tuberculosis. In the experience of these authors false positive results could be obtained when jointed connections were used in the filtration apparatus.

## HYGIENE AND PUBLIC HEALTH

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**Respiratory Immunity in Rabbits. VIII. Rabbits Immunized with Pneumonococcus Types II, III and IV Resist Intranasal Infection with Type I.**—The hope of obtaining a curative serum for pneumonia has been the chief motive power in the vast amount of work that has been done on the antigenic constitution of the pneumococcus. It was such an interest that led Neufeld to discover the fact that the serum of an animal which had been immunized with a certain strain of pneumococcus would confer passive protection against infection with this strain and also against certain other strains but not against all strains. BULL and MCKEE (*Am. J. Hyg.*, 1929, **10**, 229) claim that the fact that active immunity to the pneumococcus is not entirely type specific is of interest from a practical point of view, namely, in connection with the prophylactic vaccination of man. Vaccination against the three fixed types offers no great difficulty but the very heterogeneous nature of Group IV organisms makes it practically impossible to have all serologic types represented in a vaccine. If man reacts to pneumococci as rabbits do, it seems that vaccination with any type of pneumococcus should protect against natural infections with any other type. Rabbits immunized with pneumococcus Types II, III or IV are completely resistant to intranasal infection with Type I organisms and also manifest considerable resistance to intravenous infection with the same types.

**On the Natural Immunity to Scarlet Fever of the Japanese and Chinese Residing in South Manchuria.**—ANDO, NISHIMURA and OZAKI (*J. Immunol.*, 1929, **17**, 473) state that according to the Dick skin test there is a considerable difference in the susceptibility to scarlet fever between the Japanese and the Chinese residing in South Manchuria. The difference in scarlet fever morbidity of these two races may at least be partly explained by the difference in their susceptibility. No fact has been discovered which seems to indicate that there is a greater percentage of negative reactors among Japanese children who lived long or were born in Manchuria where scarlet fever is more prevalent than in Japan proper than among those who lived long in Japan proper and have immigrated only recently. It seems reasonable to suppose that the difference in susceptibility may indicate racial difference of "Antikorperbildungsbereitschaft" in the sense of Hirzfeld, but not dependent on the difference in "Umwelteinflusse."

# PHYSIOLOGY

PROCEEDINGS OF

THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF MARCH 17, 1930

**The Determination of the pH of Serum with the Quinhydrone Electrode.**—E. P. LAUG and D. WRIGHT WILSON (from the Department of Physiological Chemistry, University of Pennsylvania). On account of the difficulty of determining pH of body fluids by the hydrogen electrode, and certain errors encountered with the use of the colorimetric method, it seemed desirable to study the quinhydrone electrode in the hope that it might prove to be sufficiently simple and trustworthy for the pH determination of serum and plasma. A capillary quinhydrone electrode chamber was used, requiring 1 cc. serum. All determinations were done at 38° and checked with the hydrogen electrode. Considerable drift with the quinhydrone electrode occurred, but satisfactory determinations could be obtained by extrapolation. Individual extrapolated readings checked among themselves within 0.02 to 0.03 pH. In 34 determinations on the sera of 13 dogs, the quinhydrone electrode was found to average 0.02 pH more acid than the hydrogen electrode. The maximum spread of this acid correction amounted to 0.08 pH. The maximum deviation from the average amounted to 0.04 pH. Various experimental procedures caused no variation in the quinhydrone correction. It may therefore be concluded that the quinhydrone electrode may be used for pH determinations of blood serum with sufficient accuracy for most purposes.

**The Effect of Irradiated Ergosterol on the Absorption of Calcium from the Gastro-intestinal Tract.**—By J. H. JONES, M. RAPOPORT and H. HODES (from the Department of Physiological Chemistry, University of Pennsylvania). Recently it has been shown by numerous investigators that large doses of irradiated ergosterol produce a marked hypercalcemia. The source of this excess calcium has not been determined. If it comes from the body tissues it should be possible to increase the concentration of this element in the serum even though there were no calcium in the food, but if the additional calcium comes from the intestinal tract, it should be impossible to produce a hypercalcemia on a calcium-free diet.

Thirteen dogs were each given approximately 1 mg. of irradiated ergosterol per kilo per day. Seven of the animals were used as controls and were fed a diet containing about 0.25 per cent calcium, and the other six were fed a diet practically calcium free. At the end of two weeks the concentration of calcium in six of the controls ranged from 15.43 to 17.75 mg. per 100 cc. of serum, and that of the remaining control animal was 12.63 mg. The dogs on the calcium-free diet were given the ergosterol for about three weeks instead of two, at the end

of which time the concentration of calcium in five of these animals ranged from 12.41 to 13.25 mg. per 100 cc. of serum. Analyses during the three weeks period showed a very slight increase in concentration of calcium. A rather marked hypercalcemia was produced in one of the animals on the calcium-free diet, the concentration being 15.75 mg. per 100 cc. of serum at the end of the period.

Of the five animals which showed little or no hypercalcemia in three weeks, one was given "klim" and yeast at the time the ergosterol was discontinued, and daily thereafter. In six days the concentration of calcium was 15.92 mg. The other four animals were each given 20 gm. of calcium gluconate by stomach tube and in twenty hours the concentration of serum calcium ranged from 15.50 to 17.56 mg. per 100 cc. One control experiment showed no hypercalcemia at the end of twenty hours after the administration of a similar amount of the calcium salt to a dog receiving no ergosterol.

These data would indicate that the excess calcium of ergosterol hypercalcemia comes from the food, the absorption of which is increased under the influence of this drug. However, the possibility of decreased elimination has not been ruled out.

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**The Specific Cytotoxic Action of Tuberculin on Tissue Culture.**—Joseph D. Aronson (from the Henry Phipps Institute, University of Pennsylvania). The specific cytotoxic action of tuberculins prepared from the various acid-fast bacteria upon the bone marrow and the spleen of tuberculous and of nontuberculous guinea pigs was studied by means of tissue culture.

It was found that bone marrow and spleen of tuberculous guinea pigs when planted in plasma from tuberculous or nontuberculous guinea pigs fail to migrate and to multiply in concentrations of tuberculin prepared from the human or bovine type of tubercle bacillus, which also does not interfere with the migration and multiplication of the bone marrow or spleen of the nontuberculous animal. When high dilutions of tuberculin are added to bone marrow or spleen of tuberculous guinea pigs migration of cells occurs but the cells are shrunken and rounded, whereas the cells of tissue from the nontuberculous animals are irregular, larger and vesicular.

Tuberculins prepared from the avian type of tubercle bacillus, from the different acid-fast bacilli found in fish, snakes, frogs and turtle, from several different strains of the lepræ bacillus and from a number of different acid-fast saprophytes, did not interfere with the migration and multiplication of the cells from the bone marrow and from the spleen of tuberculous or of nontuberculous guinea pigs.

The specific sensitivity to tuberculin prepared from the human or bovine tubercle bacillus cannot be transferred to tissue from nontuberculous guinea pigs by the addition of plasma from a tuberculous animal.

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**The Action of Ultraviolet Rays on Sea-urchin Egg Protoplasm.**—L. V. Heilbrunn (from the Department of Zoölogy, University of Pennsylvania). In a recent monograph, I have attempted to show that when protoplasm is aroused to activity, one aspect of the response is a decided increase in viscosity. Both my older results and those of

other investigators have shown, in every case that has been suitably studied, that all protoplasmic stimulants cause such a viscosity increase. Furthermore this viscosity change is believed to be the result of a reaction (or series of reactions) which may be demonstrated to occur in widely different types of living substance, a reaction in many ways similar to that of blood clotting. This reaction, which I have called the surface precipitation reaction, typically requires calcium in its early stages.

Some years ago, Lillie and Baskervill found that the sea-urchin egg could be stimulated to divide by exposure to ultraviolet radiation. In experiments now reported on, I was able to show, (1) that such exposure to ultraviolet radiation produced a marked viscosity increase, and (2) that the radiation was only effective in the presence of calcium. Numerous tests with oxalated eggs showed complete absence of stimulation. Such eggs were not injured, and upon being returned to sea water and exposed to ultraviolet radiation, they showed the typical stimulation effect.

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**Some Results from Synchronization of Roentgen Ray Films of the Lung.**—F. MAURICE MCPHEDRAN (from the Henry Phipps Institute, University of Pennsylvania, Philadelphia). A synchronized Roentgen ray film of the lungs is an exposure made at a certain phase of the cardiac cycle. Synchronized films may be roughly divided into those that are systolic and those that are diastolic. With exposures of usual length, about one-tenth second, systolic films show blurring of the cardiac margin and of the trunk markings in the areas beside the heart, whereas in diastolic exposures the cardiac margin is sharply defined and the trunk markings are relatively clear-cut. Decrease of the length of exposure improves the sharpness of definition of both systolic and diastolic films, particularly the former, but only in patients with emphysema does the number and sharpness of the vessels recorded approach that of the excised lung. Although this appearance is no doubt partly referable to decreased density of the parenchyma relative to the density of the vascular arborization, it seems possible, from comparisons with differing techniques on young boys with thin chest walls, that change in the pulmonary elasticity is also a factor. This is also suggested by the fact that of diastolic exposures of the same person, those made with the slower heart rate show sharper pulmonary detail.

Synchronization constantly produces films more accurate than otherwise obtainable, pairs of films that are truly stereoscopic and series of films that are truly comparable. Accurate recording of pulmonary detail is conspicuously of value (1) because it gives a criterion for the comparison, from month to month, of the relative density of early lesions based on the pleura (for example, adolescent tuberculosis); (2) because upon and between the pulmonary markings, particularly in the base, appear the infiltrations of the childhood type of tuberculosis and nontuberculous lesions at all ages. In the discovery and supervision of these basal lesions, particularly the slighter ones, accurate comparable and truly stereoscopic films are essential. Synchronizing both exposures to occur in diastole affords stereoscopy of the cardiac and paracardiac areas and permits recognition of slight infiltrations

that appear as spots upon or between the vascular markings or, in the more chronic stages, cause irregular emphasis and distortion of vascular detail. Without control of the time of exposure with relation to the cardiac phase, truly stereoscopic films are a matter of chance. Even a small amount of cardiac movement, as revealed by a blurred heart border, may render a small infiltration wholly imperceptible.

Synchronization provides films that may be compared with and interpreted in the light of pathologic study of excised lungs that have been Roentgen rayed while inflated. It has made it possible define the limits of recordability of enlarged nodes within the hilum and, in eliminating artefacts due to movement, has clarified many confusing appearances.

In summary, synchronization has proved of material aid in adapting the Roentgen rays to the discovery of changes in pulmonary density. Except when wholly hidden by opaque structures, such as heart and diaphragm, and this is unusual, synchronized stereoscopic films record with fair accuracy those pathologic changes of the parenchyma that are sufficient to be the cause of symptoms and also latent lesions. Furthermore, they assist in defining the pathologic structure and direction of change of tuberculous and most nontuberculous infiltrations, and they are, therefore, a record of the anatomical stability of a lesion, without which arrest and cure are illusory.

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